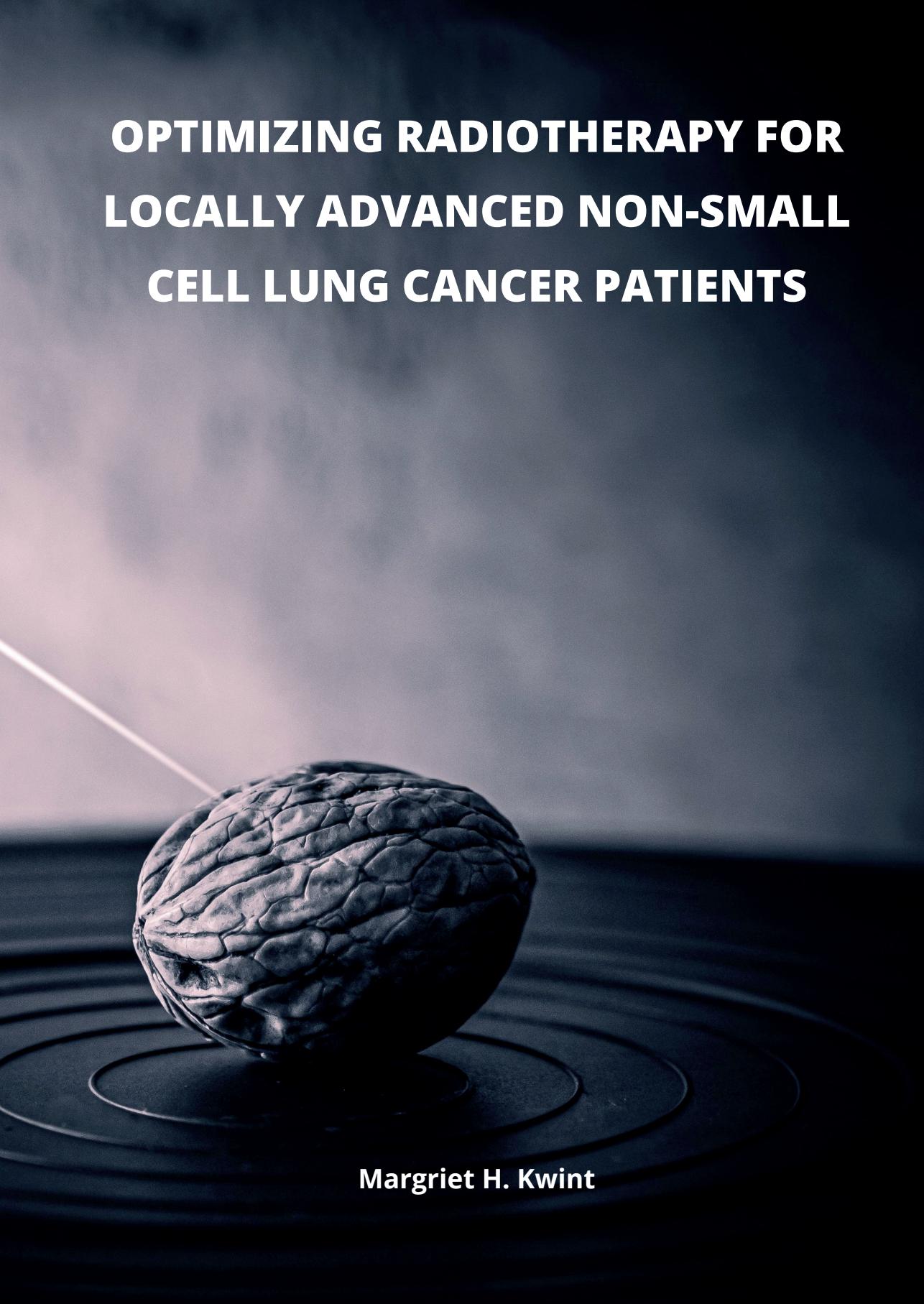
OPTIMIZING RADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS



Margriet H. Kwint

OPTIMIZING RADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

Margriet H. Kwint

The work described in this thesis was performed at the Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, The Netherlands

ISBN: 978-94-6416-441-1
Cover design: Bernice Timmers
Lay-out: Publiss | www.publiss.nl
Print: Ridderprint | www.ridderprint.nl

Financial support for printing of this thesis has kindly been provided by The Netherlands Cancer Institute – Antoni van Leeuwenhoek, ChipSoft and Boehringer Ingelheim bv

VRIJE UNIVERSITEIT

OPTIMIZING RADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor

aan de Vrije Universiteit Amsterdam,

op gezag van de rector magnificus

prof.dr. V. Subramaniam

in het openbaar te verdedigen

ten overstaan van de promotiecommissie

van de Faculteit der Geneeskunde

op dinsdag 18 mei 2021 om 9.45 uur

in de aula van de universiteit,

De Boelelaan 1105

door

Margriet Henrianne Kwint

geboren te Assen

promotoren:	prof.dr. M. Verheij
	prof.dr.ir J.-J. Sonke
copromotoren:	dr. J.S.A. Belderbos
	dr. I. Walraven

Voor mijn lieve ouders

Table of Contents:

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THESIS

General aspects of Lung Cancer

Lung cancer is one of the most commonly occurring cancers in the world, with approximately 2 million new patients in 2018 (1). The global epidemic of lung cancer is primarily caused by tobacco smoking (2, 3), accounting for 80-90% of lung cancer cases (2). Lung cancer has a high mortality rate in the Netherlands; only 19% of the patients are alive 5 years after diagnosis (based on the period 2011-2015) (4). In 2018, 13.800 people were newly diagnosed with lung cancer in the Netherlands (4). Lung cancer is generally divided into 2 major subtypes; Non-Small Cell Lung Cancer (NSCLC, 80%) and Small Cell Lung Cancer (SCLC, 15%). SCLC-patients have the worst prognosis with a 5 year overall survival (OS) of 8% compared to 20% for NSCLC (4). Lung cancer is staged based on the TNM principle: extension of the primary tumor (T-stage), involved lymph nodes (N-stage) and presence of distant metastasis (M-stage) (5). When there is a large primary tumor and/or involvement of mediastinal lymph nodes, but without distant metastasis, it is defined as Locally-Advanced Non-Small Cell Lung Cancer (LA-NSCLC), also known as stage III. About 25% of all NSCLC patients present with LA-NSCLC at diagnosis. This stage is often inoperable due to local or regional tumor extension. Therefore, these patients are often treated with a combination of systemic treatment and radical radiotherapy. This thesis focused on studies to optimize radiotherapy for patients with LA-NSCLC.

Treatment of locally advanced NSCLC

Since the mid-1990s, the standard treatment for LA-NSCLC has been thoracic radiotherapy. After the meta-analysis of the Non-Small Cell Lung Cancer Collaborative Group in 1995 (6), the value of additional chemotherapy was established. An absolute OS benefit of 10%, 4% and 5% for 1, 2 and 5 years respectively, was reported in this meta-analysis in favor of radiotherapy combined with chemotherapy compared to radiotherapy alone. In 2010, a meta-analysis (7) showed an absolute OS benefit of 5.7% and 4.5% at 3 and 5 years for concurrent chemoradiation (CCRT) compared to sequential chemoradiation (SCRT). Currently, for patients with LA-NSCLC, the treatment of choice is CCRT (7, 8). Nonetheless, with 2-year OS rates ranging between 44 and 59%, there is certainly room for improvement (9-11). Recently, a phase III trial investigating the potential benefits from adjuvant immunotherapy after CCRT in LA-NSCLC patients, reported significant improvements of progression free survival (PFS) (median PFS 5.6 months versus 17.2 months) and OS (2-year OS 55.6% versus

66.3%) (12). Therefore, adjuvant immunotherapy after CCRT, in patients without tumor progression, is standard of care in the Netherlands since 2019. The studies described in this thesis have included patients who were treated between 2008 and 2017, when CCRT alone was standard of care for LA-NSCLC.

NSCLC is a heterogeneous disease and together with the increase of treatment options such as chemotherapy, molecular targeted agents, immunotherapy, optimized radiotherapy schemes/techniques, and new surgery techniques, it is important to select the best treatment (or combinations) for each individual patient. Moreover, the emergence of novel parameters such as genomics, imaging modalities and new biomarkers calls for more innovative models to depict the best treatment for each patients, while taking into account several interdependencies between risk markers. Current prediction models use baseline characteristics to predict treatment outcomes (13). The use of baseline characteristics only, currently limits these models to a moderate predictive accuracy. A major improvement might be to incorporate novel longitudinal risk parameters into dynamic models that can be updated during treatment and/or follow-up. Such dynamic models can serve personalized treatment choices, e.g. to distinguish in which patient a resection after CCRT needs to be considered.

Optimization of radiotherapy by dose alteration

With the theory that increasing the radiotherapy dose improves local control and OS, dose-escalation is an appealing option (14, 15). The excellent local control and OS reported for limited stage NSCLC patients treated with stereotactic ablative radiotherapy (SABR) (16) substantiates this theory. Safety and efficacy of dose escalation for LA-NSCLC was studied in several studies (9, 14, 17-20). A large phase III trial (RTOG-0617) (9) reported worse OS for the high dose arm (74 Gy, 2Gy fractions) compared to the standard arm (60 Gy, 2Gy fractions); 20.3 versus 28.7 months respectively. Furthermore, an increase of acute toxicity was seen in the dose-escalation arm. A recent Swedish randomized dose escalation phase II trial (19) (68 Gy versus maximum 84 Gy in 2 Gy per fraction) was prematurely terminated (N=36, 18 in each arm) due to excessive toxicity; 7 toxicity related death due to esophageal perforations and pneumonitis of which 5 in the dose-escalated arm and 2 in the standard arm. In both studies, dose escalation was performed by extending the overall treatment time. Since the outcomes of these recent trials, there is common

opinion that dose escalation with prolonged overall treatment time is not effective. Therefore, hypofractionation should be used in further studies focusing on dose-escalation. In our institute a mildly hypofractionated radiotherapy schedule is used of 24x2.75 Gy, once daily, 5 times a week (17). Compared to the conventional schedule of 60 Gy in 30 fractions, this hypofractionated schedule results in a reduction of more than one-week overall treatment time; 32 days versus 40 days. Besides, a higher biological effective dose is given, with the expectation of improved local control. The type of chemotherapy administered for concurrent chemotherapy varies across centers in the Netherlands (21). Due to the advantageous toxicity profile, daily low dose Cisplatin is preferred in the Netherlands Cancer Institute. Several studies (10, 17, 18, 20, 22) reported a high local control and a low toxicity of this CCRT-regime. It is well known that local control is associated with OS in lung cancer. Van Diessen et.al (22) investigated the pattern of local and regional failure in LA-NSCLC patients treated with CCRT. The incidence of local and regional failure as site of first failure was 16% and 6%, respectively. This difference was significantly associated with the difference in volume of the primary tumor and lymph nodes. The risk of severe pulmonary, cardiac and esophageal toxicities induced by CCRT, are mainly determined by the involvement of the mediastinal lymph nodes, the size and location of the primary tumor and the total radiation dose. Since involved mediastinal lymph nodes have generally a smaller volume compared to the primary tumor in the majority of patients, an appealing strategy is to prescribe a differentiated dose to the lymph nodes and primary tumor to reduce acute and late toxicities in LA-NSCLC patients treated with CCRT.

Patient selection for oligometastatic disease

When a NSCLC patient is diagnosed with metastases, from a historical point of view, the treatment aim is palliative; to prolong PFS or to improve quality of life. In 1995, the term 'oligometastasis' was introduced by Hellman and Weichselbach (23). This concept implies that patients with a limited number of metastases might still achieve long term OS if all these metastases are treated with a radical schedule (24-26). With more systemic treatment options for NSCLC patients (e.g. molecular targeted therapies and immune checkpoint inhibitors) (27), there is an increasing interest in a more radical approach for oligometastatic disease (28-30). SABR is a highly advanced radiotherapy technique, which is able to deliver very precisely a high biologically effective dose to a small tumor (31). SABR is a very effective treatment with few side effects, to treat

(oligo) metastases in for example brain, liver, lungs, bone and adrenal glands. Besides SABR, radiofrequency ablation and surgery are also frequently used techniques to treat (oligo) metastases. Between 2008 and 2016 we performed an observationally study in patients that were selected during a tumor board meeting to have a radical approach of oligometastatic NSCLC (32). In this time period a radical approach for oligo metastatic NSCLC was not standard of care (28, 33). Recent years, evidence is growing that a radical treatment for oligometastatic NSCLC is beneficially. Recently published phase 2 trials, showed a significantly improved OS in oligometastatic NSCLC patients who were treated with a radical treatment on all metastases (26, 30). At the moment, phase 3 studies are ongoing (34, 35) to establish the role of such a radical approach in NSCLC finally. This will hopefully gather evidence, to confirm the benefit seen in randomized phase II trials of this therapeutic approach for oligometastatic disease, and will teach us which patient to select.

Image Guided radiotherapy

The introduction of the ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT, had a major impact on accurate staging of lung cancer patients. An FDG-PET is able to differentiate between an elevated glucose metabolism in tissues, which is characteristic for cancer and inflammation, and leads to a more accurate tumor staging; e.g. a better distinction between tumor and atelectasis or detection of distant metastasis (36). By combining the FDG-PET with the RT-planning CT, the delineation uncertainties of the gross tumor volume (GTV) are reduced (37). To take into account microscopic tumor extension, the GTV is expanded to the clinical target volume (CTV). To correct for geometric uncertainties, this CTV is expanded to a planning target volume (PTV) (38). In our institute the 'van Herk' margin recipe is used (39), which corrects for random and systemic errors and incorporates the size of the margin on individualized respiratory tumor motion.

Image guide radiotherapy (IGRT) visualizes the tumor and organs at risk (OAR) in the treatment room and corrects for differences between treatment planning and delivery. In the past, electronic portal imaging devices (EPID) with the use of megavolt or kilovolt imaging were used making 2D images. Nowadays most modern radiotherapy departments use linear accelerator integrated Cone Beam CT's (CBCT) for imaging during radiotherapy (40). A CBCT is a type of CT-scanner, which can make in-room 3D and 4D (kV) images of the patient before, during and after the treatment using a single

rotation. The images made by the CBCT are registered to the images of the RT-planning CT based on anatomical structures (e.g. vertebrae, carina or the primary tumor). This registration can be used for tumor alignment, to observe anatomical changes and for dosimetric purposes (41). The accuracy of radiotherapy is affected by a diversity of geometrical uncertainties (e.g. set-up errors, baseline shifts and respiratory motion). The goal of IGRT is to increase this accuracy during a radiotherapy fraction (intra-fraction) and between different fractions (inter-fraction). The repetitive CBCT's made us also aware of intra thoracic anatomical changes during treatment in lung cancer. In the Netherlands, CBCT's are typically analyzed by radiation therapy technician (RTT); the radiation oncologist is informed in case a change is observed. With the increased use of daily CBCT imaging, there was a clinical need for a clear and practical decision support system to guide the RTTs in prioritizing the anatomical changes. Since 2012, daily CBCT's with online position verification and correction are made for lung cancer patients treated with radical intent in the Netherlands Cancer Institute. Schaake et al. (42) demonstrated that the PTV margins can be reduced when this daily online CBCT position verification is used. Subsequently, a PTV margin reduction with expected decrease in toxicity was clinically introduced in 2015 in our institute.

These daily CBCT's also resulted in an increase of imaging data of tumor volume changes during treatment. The predictive value of tumor volume changes has been studied previously (43-45). These studies hint towards a predictive potential for OS, when there was tumor volume change during treatment, but the observed associations were inconsistent and the performed studies included few patients. Furthermore, the performed analyses could have been too simplistic. For example, observed GTV-changes during treatment were dichotomized below or above the median (43-45). The assumption that 2 groups (above/below median) represent the treatment response of all NSCLC patients might be a misconception (46). In order to identify various subgroups of patients with distinct treatment responses, more advanced statistical techniques, such as latent class mixed modelling, could be useful (47-50). Hence, more research is needed to analyze the predictive potential of tumor volume change during radiotherapy for treatment outcome.

Acute esophagus toxicity

The addition of chemotherapy concurrent with radiotherapy provokes a radiosensitizing effect leading to an improved local tumor control and OS, compared

to radiotherapy only or sequential chemoradiation (7). However, this comes at the cost of radiotherapy induced pulmonary, cardiac and esophageal toxicities. Toxicity in radiotherapy can be divided in acute (≤ 90 days after end of treatment) or late toxicity (> 90 days after end of treatment). A common radiotherapy induced toxicity is acute esophagus toxicity (AET) (51). This leads to decreased intake, weight loss, malnutrition and retrosternal pain, requiring analgesics, intravenous hydration, tube feeding, dietary supplements, hospitalization or a combination of these. To inform a patient thoroughly about the risk on toxicities before start of treatment, it is important that the normal tissue complication probability models (NTCP-models) clinically used to predict the risk on toxicities, are accurate. Several NTCP-models are used in clinical practice to predict the risk of AET (51-56). However, many of these models are based on 3D-conformal radiotherapy (3D-CRT) techniques. With the introduction of newer radiotherapy techniques like Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), a more conformal dose distribution can be achieved (57, 58). These techniques give the opportunity to irradiate larger tumor volumes and increase organ sparing compared to 3D-CRT (59-61). However, this might result in dose inhomogeneity, which can lead to e.g. high dose areas in organs at risk, which are situated inside the PTV such as the esophagus. In addition, an increase of larger low dose areas in healthy tissue is frequently seen with IMRT and/or VMAT. This is due to the use of segments and greater amount of beam directions compared to 3D-CRT. Hence, patients who were not eligible for a radical radiotherapy schedule because of large tumor volumes in the 3D-CRT era, benefit due to IMRT and VMAT, and may be able to receive radiotherapy with a curative intent. These improvements in radiation dose characteristics have influence on the predictive performance of dose limiting toxicities, such as AET, of NTCP models. Therefore, the development of these new radiotherapy techniques and schedules requires a constant validation and update of the existing NTCP-models.

Purpose and outline of thesis

The primary aim of this thesis is to optimize radiotherapy for LA-NSCLC patients further. This aim is achieved by focusing on different aspects of the radiation treatment. The first part focused on the effect of margin reduction and dose de-escalation of the dose on the mediastinal lymph nodes on toxicity and treatment outcome. Furthermore, we analyzed patients with oligo metastasized NSCLC that qualified for a radical treatment. The second part focused on imaging data of intra

thoracic and tumor volume changes collected during treatment on CBCT and its association with treatment outcome. In the last part of this thesis the prediction models of acute esophagus toxicity after CCRT are optimized.

Part I Dose prescription and patient selection

Subject of the studies in the first part of this thesis is optimizing the treatment of LA-NSCLC patients by adapting treatment dose prescription and execution. Since June 2015, patients with LA-NSCLC are treated in our institute with a differentiated dose to the primary tumor and involved mediastinal lymph nodes. Simultaneously, the planning margins for both the primary tumor and the lymph nodes are reduced. We also changed the patient selection by treating patients with oligometastatic disease with a radical irradiation scheme.

In **chapter 2,** the treatment outcome of the dose de-escalation and margins reductions to the lymph nodes and the effects on the incidence of toxicities of this dose de-escalation are studied in a large retrospective cohort.

In **chapter 3,** the PFS and OS of oligometastatic NSCLC patients selected for a treatment with radical intent are described.

Part II Image Guided Radiotherapy

With the increasing use of image guided radiotherapy for NSCLC patients, longitudinal imaging data of tumor volume reduction during the course of a radiotherapy treatment is available and intra thoracic anatomical changes are frequently detected.

In **chapter 4,** the incidence of the different intra thoracic anatomical changes detected on CBCT during radiotherapy is described and a practical decision support system is introduced.

In **chapter 5,** the association of tumor volume changes, detected on CBCT during concurrent chemoradiation for LA-NSCLC patients, with treatment outcome is studied.

Part III Acute esophagus toxicity

In the last part of this thesis, prediction models for acute esophagus toxicity (AET) were analyzed and optimized after CCRT. Toxicity is nowadays scored in an electronic toxicity registration in the electronic medical record at the NKI, and with that, the (real world) data of treatment related toxicity can accordingly much easier be collected compared to the analog medical record. This real world data of toxicity scoring can be used for auditing toxicity prediction models.

In **chapter 6,** the dose effect relation of AET and dose volume parameters of the esophagus for patients treated with CCRT are investigated. In this study, NTCP-models of AET of IMRT are compared with 3D-CRT.

In **chapter 7,** the validity of real world data derived from an electronic toxicity registration is assessed. The electronic toxicity registration of AET before and after dose-de-escalation for the 2 cohorts as described in **chapter 2** are used to validate the NTCP-models of AET for CCRT for NSCLC patients.

The general discussion and future perspective of this thesis are described in **chapter 8.**

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e1S-e29S.
3. Jayes L, Haslam PL, Gratziou CG, Powell P, Britton J, Vardavas C, et al. SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health. Chest. 2016;150(1):164-79.
4. https://www.iknl.nl/nkr-cijfers.
5. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
6. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ. 1995;311(7010):899-909.
7. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-90.
8. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010(6):CD002140.
9. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.
10. Dieleman EMT, Uitterhoeve ALJ, van Hoek MW, van Os RM, Wiersma J, Koolen MGJ, et al. Concurrent daily Cisplatin and high dose radiotherapy in patients with stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2018.
11. Walraven I, van den Heuvel M, van Diessen J, Schaake E, Uyterlinde W, Aerts J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Radiother Oncol. 2016;118(3):442-6.
12. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Brief report: Three-year overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC - Update from PACIFIC. J Thorac Oncol. 2019.
13. Oberije C, De Ruysscher D, Houben R, van de Heuvel M, Uyterlinde W, Deasy JO, et al. A Validated Prediction Model for Overall Survival From Stage III Non-Small Cell Lung Cancer: Toward Survival Prediction for Individual Patients. Int J Radiat Oncol Biol Phys. 2015;92(4):935-44.

14. Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys. 2005;63(2):324-33.
15. van Baardwijk A, Bosmans G, Boersma L, Wanders S, Dekker A, Dingemans AM, et al. Individualized radical radiotherapy of non-small-cell lung cancer based on normal tissue dose constraints: a feasibility study. Int J Radiat Oncol Biol Phys. 2008;71(5):1394-401.
16. Fernandez C, Grills IS, Ye H, Hope AJ, Guckenberger M, Mantel F, et al. Stereotactic Image Guided Lung Radiation Therapy for Clinical Early Stage Non-Small Cell Lung Cancer: A Long-Term Report From a Multi-Institutional Database of Patients Treated With or Without a Pathologic Diagnosis. Pract Radiat Oncol. 2019.
17. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). Eur J Cancer. 2007;43(1):114-21.
18. Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66(1):126-34.
19. Hallqvist A, Bergstrom S, Bjorkestrand H, Svard AM, Ekman S, Lundin E, et al. Dose escalation to 84 Gy with concurrent chemotherapy in stage III NSCLC appears excessively toxic: Results from a prematurely terminated randomized phase II trial. Lung Cancer. 2018;122:180-6.
20. Uyterlinde W, Belderbos J, Baas C, van Werkhoven E, Knegjens J, Baas P, et al. Prediction of acute toxicity grade >/= 3 in patients with locally advanced non-small-cell lung cancer receiving intensity modulated radiotherapy and concurrent low-dose Cisplatin. Clin Lung Cancer. 2013;14(5):541-8.
21. Walraven I, Damhuis RA, Ten Berge MG, Rosskamp M, van Eycken L, de Ruysscher D, et al. Treatment Variation of Sequential versus Concurrent Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer Patients in the Netherlands and Belgium. Clin Oncol (R Coll Radiol). 2017.
22. van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential analysis of local and regional failure in locally advanced non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Radiother Oncol. 2016;118(3):447-52.
23. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995;13(1):8-10.
24. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state - separating truth from wishful thinking. Nat Rev Clin Oncol. 2014;11(9):549-57.
25. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. J Thorac Oncol. 2019;14(12):2109-19.
26. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18-e28.

27. Osmani L, Askin F, Gabrielson E, Li QK. Current WHO guidelines and the critical role of immunohistochemical markers in the subclassification of non-small cell lung carcinoma (NSCLC): Moving from targeted therapy to immunotherapy. Semin Cancer Biol. 2018;52(Pt 1):103-9.
28. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol. 2012;7(10):1547-55.
29. Gomez DR, Tang C, Zhang J, Blumenschein GR, Jr., Hernandez M, Lee JJ, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37(18):1558-65.
30. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051-8.
31. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol. 2014;32(26):2847-54.
32. Kwint M, Walraven I, Burgers S, Hartemink K, Klomp H, Knegjens J, et al. Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases. Lung Cancer. 2017;112:134-9.
33. Gomez DR, Blumenschein GR, Jr., Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17(12):1672-82.
34. Palma DA, Olson R, Harrow S, Correa RJM, Schneiders F, Haasbeek CJA, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. BMC Cancer. 2019;19(1):816.
35. E²-RADIatE: EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe (E²-RADIatE). Available online: https://clinicaltrials.gov/ct2/show/NCT03818503.
36. Grootjans W, de Geus-Oei LF, Troost EG, Visser EP, Oyen WJ, Bussink J. PET in the management of locally advanced and metastatic NSCLC. Nat Rev Clin Oncol. 2015;12(7):395-407.
37. Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF, et al. Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis. Int J Radiat Oncol Biol Phys. 2006;64(2):435-48.
38. Hodapp N. [The ICRU Report 83: prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT)]. Strahlenther Onkol. 2012;188(1):97-9.
39. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. Int J Radiat Oncol Biol Phys. 2000;47(4):1121-35.

40. Borst GR, Sonke JJ, Betgen A, Remeijer P, van Herk M, Lebesque JV. Kilo-voltage cone-beam computed tomography setup measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device. Int J Radiat Oncol Biol Phys. 2007;68(2):555-61.
41. Sonke JJ, Zijp L, Remeijer P, van Herk M. Respiratory correlated cone beam CT. Med Phys. 2005;32(4):1176-86.
42. Schaake EE, Rossi MM, Buikhuisen WA, Burgers JA, Smit AA, Belderbos JS, et al. Differential motion between mediastinal lymph nodes and primary tumor in radically irradiated lung cancer patients. Int J Radiat Oncol Biol Phys. 2014;90(4):959-66.
43. Brink C, Bernchou U, Bertelsen A, Hansen O, Schytte T, Bentzen SM. Locoregional control of non-small cell lung cancer in relation to automated early assessment of tumor regression on cone beam computed tomography. Int J Radiat Oncol Biol Phys. 2014;89(4):916-23.
44. Jabbour SK, Kim S, Haider SA, Xu X, Wu A, Surakanti S, et al. Reduction in Tumor Volume by Cone Beam Computed Tomography Predicts Overall Survival in Non-Small Cell Lung Cancer Treated With Chemoradiation Therapy. Int J Radiat Oncol Biol Phys. 2015;92(3):627-33.
45. Wald P, Mo X, Barney C, Gunderson D, Haglund AK, Bazan J, et al. Prognostic Value of Primary Tumor Volume Changes on kV-CBCT during Definitive Chemoradiotherapy for Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2017;12(12):1779-87.
46. Walraven I, Kwint M, Belderbos J. The Additional Prognostic Value of Tumor Volume Changes during Chemoradiotherapy in Patients with Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(9):e181-e2.
47. Proust-Lima C, Sene M, Taylor JM, Jacqmin-Gadda H. Joint latent class models for longitudinal and time-to-event data: a review. Stat Methods Med Res. 2014;23(1):74-90.
48. Proust-Lima C, Taylor JM. Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: a joint modeling approach. Biostatistics. 2009;10(3):535-49.
49. Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol. 2012;65(10):1078-87.
50. Walraven I, Mast MR, Hoekstra T, Jansen AP, van der Heijden AA, Rauh SP, et al. Distinct HbA1c trajectories in a type 2 diabetes cohort. Acta Diabetol. 2015;52(2):267-75.
51. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87(4):690-6.
52. Dankers F, Wijsman R, Troost EGC, Tissing-Tan CJA, Kwint MH, Belderbos J, et al. External validation of an NTCP model for acute esophageal toxicity in locally advanced NSCLC patients treated with intensity-modulated (chemo-)radiotherapy. Radiother Oncol. 2018;129(2):249-56.
53. Dehing-Oberije C, De Ruysscher D, Petit S, Van Meerbeeck J, Vandecasteele K, De Neve W, et al. Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. Radiother Oncol. 2010;97(3):455-61.

54. Kwint M, Uyterlinde W, Nijkamp J, Chen C, de Bois J, Sonke JJ, et al. Acute esophagus toxicity in lung cancer patients after intensity modulated radiation therapy and concurrent chemotherapy. Int J Radiat Oncol Biol Phys. 2012;84(2):e223-8.
55. Rose J, Rodrigues G, Yaremko B, Lock M, D'Souza D. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol. 2009;91(3):282-7.
56. Belderbos J, Heemsbergen W, Hoogeman M, Pengel K, Rossi M, Lebesque J. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol. 2005;75(2):157-64.
57. Grills IS, Yan D, Martinez AA, Vicini FA, Wong JW, Kestin LL. Potential for reduced toxicity and dose escalation in the treatment of inoperable non-small-cell lung cancer: a comparison of intensity-modulated radiation therapy (IMRT), 3D conformal radiation, and elective nodal irradiation. Int J Radiat Oncol Biol Phys. 2003;57(3):875-90.
58. Bezjak A, Rumble RB, Rodrigues G, Hope A, Warde P, Members of the IIEP. Intensity-modulated radiotherapy in the treatment of lung cancer. Clin Oncol (R Coll Radiol). 2012;24(7):508-20.
59. Chapet O, Fraass BA, Ten Haken RK. Multiple fields may offer better esophagus sparing without increased probability of lung toxicity in optimized IMRT of lung tumors. Int J Radiat Oncol Biol Phys. 2006;65(1):255-65.
60. Chapet O, Thomas E, Kessler ML, Fraass BA, Ten Haken RK. Esophagus sparing with IMRT in lung tumor irradiation: an EUD-based optimization technique. Int J Radiat Oncol Biol Phys. 2005;63(1):179-87.
61. Schwarz M, Alber M, Lebesque JV, Mijnheer BJ, Damen EM. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2005;62(2):561-70.

CHAPTER 2

SAFETY AND EFFICACY OF REDUCED DOSE AND MARGINS TO INVOLVED LYMPH NODE METASTASES IN LOCALLY ADVANCED NSCLC PATIENTS

Margriet H. Kwint*, Judi N.A. van Diessen*, Jan-Jakob Sonke, Iris Walraven, Barbara Stam, Adrianus J. de Langen, Joost Knegjens, José S.A. Belderbos

***Both authors contributed equally to this paper.**

Radiother Oncol. 2020;143:66-72. doi:10.1016/j.radonc.2019.07.028

Background and purpose

(Chemo)Radiotherapy for locally advanced non-small lung cancer (LA-NSCLC) causes severe dysphagia due to the radiation dose to the mediastinal lymphadenopathy. Reducing the dose to the mediastinum and the margins to the planning target volume (PTV) might reduce severe toxicity rates. The results of both adaptations in LA-NSCLC patients receiving (chemo) radiotherapy were analysed.

Materials and methods

Three hundred and eight LA-NSCLC patients were included in an observational study. Both cohorts received hypofractionated RT (24x2.75 Gy) of 70 Gy ($EQD2_{10}$) to the primary tumour. The reference-cohort (N=170) received the same dose of 70 Gy ($EQD2_{10}$) to the involved lymph nodes, while the reduction-cohort (N=138) received 24x2.42 Gy, biologically equivalent to 60 Gy ($EQD2_{10}$). Furthermore, the patient-specific PTV-margins for both the primary tumour and lymph nodes were reduced by 2-3mm in the reduction-cohort after implementing a carina based correction strategy. The effects on toxicity, regional failure and overall survival (OS) were assessed.

Results

The acute grade 3 (G3) dysphagia and G3 pulmonary toxicity decreased significantly from 12.9% to 3.6% and 4.1% versus 0%, respectively. The regional failures were comparable: 5.9% versus 4.3% (p=0.546). The median OS was significantly different: 26 months (reference-cohort) versus 35 months (reduction-cohort). After correction for confounders, the association between the reduction-cohort and OS remained significant (HR 0.63 versus HR 0.70).

Conclusion

A reduction in PTV-margins and dose from 70 Gy to 60 Gy to the involved lymph nodes in LA-NSCLC patients receiving (chemo) radiotherapy did not result in an increase in regional failures. Moreover, significantly lower acute toxicities and an improved OS were observed in the reduction-cohort.

Introduction

Concurrent chemoradiotherapy (cCRT) for locally advanced non-small cell lung cancer (LA-NSCLC) results in a 5-year overall survival (OS) of 32% [1, 2]. Local and regional failures as well as severe acute and late toxicities adversely affect OS [1, 3, 4]. Determining the balance between optimal treatment outcomes and low toxicity rates is challenging. The risk of severe pulmonary, oesophageal and cardiac toxicity is mainly determined by the involvement of mediastinal lymph nodes, the size and location of the primary tumour and the total radiation dose [3, 5-7]. Dose-limiting toxicities include radiation pneumonitis, associated with mean lung dose (MLD), and severe acute and late dysphagia (grade 3 and higher), associated with the volume of the oesophagus receiving >50-60 Gy [8, 9]. Moreover, the RTOG-0617 trial demonstrated an association of heart dose and OS [1]. Similar findings were found in various other cohorts [10, 11]. The reported incidence of regional failures (RF) after radiotherapy for LA-NSCLC was generally lower than local failures (LF), around 10% versus 30% after 2 years [12-14]. We reported on prognostic factors predicting LF and RF after cCRT in detail, revealing that volume was the only significant factor [12]. Since involved mediastinal lymph nodes have a smaller volume compared to the primary tumour in the majority of patients, we hypothesized that the dose needed to control lymph node metastases might be lower than the dose needed to control the primary tumour. A consequence of a lower dose to the mediastinum might also induce an efficient reduction of the pulmonary, oesophageal and cardiac toxicity rates. Additionally, further decrease of the toxicity rates might be obtained by a margin reduction. Previously, Schaake et al. demonstrated that the planning target volume (PTV) margins for the tumour and the lymph nodes might be reduced due to a daily online carina based correction strategy [15]. Since June 2015, patients with LA-NSCLC were treated in our institute to a lower radiotherapy dose to the involved mediastinal lymph nodes of 58 Gy (24x2.42 Gy; $EQD2_{10}$=60 Gy), while the primary tumour was treated with 66 Gy (24x2.75 Gy; $EQD2_{10}$=70 Gy) by using a simultaneous integrated boost technique. Simultaneously, the planning margins for both the primary tumour and the lymph nodes were reduced. The aim of this study is to investigate the effects of this reduction of dose to the involved lymph nodes and PTV-margins on the incidence of toxicities and outcomes.

Material and methods

Patient selection

A sequential design cohort study was performed including 308 patients with LA-NSCLC between June 2013 and June 2017. All data were analysed retrospectively. Patient characteristics, treatment data and medical records were also retrospectively retrieved. Standard work-up consisted of a computed tomography (CT)-thorax, a total body ^{18}Fluorodeoxyglucose positron emission tomography (FDG-PET)-CT-scan (performed within 4-6 weeks before treatment according to the NedPass protocol [16]), a contrast enhanced CT-scan or Magnetic Resonance Imaging (MRI)-scan of the brain and a pulmonary function test. Pathological confirmation of the primary tumour and/or lymph nodes was done. All pre- and post-treatment diagnostic examinations were available for all patients. The Institutional Review Board of our institute approved the study for retrospective data collection according to the European Privacy Law.

Radiotherapy preparation

Patients were treated with hypofractionated Intensity Modulated Radiotherapy (IMRT) of 66 Gy to the primary tumour and mediastinal lymph nodes in 24 fractions (overall treatment time 32 days), once daily, 5 times per week from June 2013 till June 2015. Following the linear-quadratic model and an α/β-ratio of 10 Gy, an absorbed dose of 66 Gy in 24 fractions is biologically equivalent to 70 Gy in fractions of 2 Gy ($EQD2_{10}$). From June 2015, the dose to the involved mediastinal lymph nodes was reduced from 66 Gy to 58.08 Gy in 24 fractions, which is equivalent to 60 Gy ($EQD2_{10}$). Therefore, the dataset was divided in two cohorts: the reference-cohort versus the reduction-cohort. Treatment consisted of sequential chemoradiotherapy (sCRT), cCRT or radiotherapy (RT) only. The concurrent regimen consisted of daily low dose Cisplatin intravenous (6 mg/m², maximum 12 mg) 1-2 hours before each RT fraction. The chemotherapy in sCRT consisted of Cis- or Carboplatin combined with Gemcitabin, Etoposide or Pemetrexed according to the pathology. A four-dimensional (4D)-CT-scan with intravenous contrast was performed, from which a 3D-midposition-CT-scan (MidP) was reconstructed [17]. The FDG-PET-CT-scan was registered with the MidP to guide the separate delineation of the primary tumour and the involved lymph nodes. The following lymph nodes were considered tumour positive in the absence of pathological evidence: higher FDG-uptake than the mediastinal blood pool on the FDG-PET-CT-scan or growth on

the CT compared to the baseline CT. The gross tumour volume (GTV) of the primary tumour as well as the GTV of the lymph nodes were both expanded to a planning target volume (PTV). Subsequently, the PTV-margins were individualized according to the peak-to-peak respiratory amplitude movement of the tumour and lymph nodes. The margins in all directions from GTV to PTV consisted of 12 mm plus ¼ of the peak-to-peak amplitude in orthogonal directions as measured in the 4D-CT [18]. An isotropic PTV margin of 12 mm was used for the lymph nodes. The PTV-margins were adapted from June 2015 when a bony anatomy based correction strategy was replaced with a carina based correction strategy on the CBCT [15]. Reduction of the PTV-margins was applicable to all directions with a maximum in the cranio-caudal direction of 3.8mm for the lymph nodes and 2.1mm for the primary tumour. From then on, the PTV-margins varied between 9-11 mm. The following organs at risk (OAR) were delineated according to our institutional protocol: heart, spinal cord, lungs and oesophagus. For this study, the heart (sub)structures were delineated automatically using an automatic segmentation method [10]. The planning constraints were: oesophagus D_{max} ≤66 Gy and V_{50Gy} ≤50% ($EQD2_{10}$), MLD ≤20 Gy ($EQD2_3$), spinal cord ≤52 Gy ($EQD2_2$), total heart ≤40 Gy and ⅔ of the heart ≤50 Gy and ⅓ of the heart ≤66 Gy ($EQD2_3$). IMRT-plans were calculated using 10 MV photons. Dose distributions were calculated using collapsed cone inhomogeneity corrections (Pinnacle versions 9.2-9.10, Philips, Best, The Netherlands). The dose inhomogeneity within the PTV was between the 90% and 115%. Treatment verification was done using daily cone beam CT-scans (CBCT) according to an on-line setup correction protocol and correction was performed immediately before the start of every fraction. Replanning was done in case of significant changes of the anatomy with an anticipated clinically relevant influence on the dose distribution [19].

Toxicity and follow-up (FU)

Toxicity was scored using the Common Toxicity Criteria for Adverse Events version 4.0. Acute toxicity was scored from start of RT until 3 months after the last fraction. Late toxicity was calculated from 3 months after the last fraction. A CT-thorax was performed 6-8 weeks after treatment to evaluate the treatment response. Subsequently, FU was performed every 3-6 months with chest X-ray or CT-thorax. After 2 years, FU was performed every 6 months.

Treatment outcome

LF and RF were defined as an in-field failure within the PTV of the primary tumour (LF) and the involved lymph nodes (RF). In both cases, pathologic confirmation or an increase in tumor diameter of at least 20% compared to the previous CT-scan was scored as a failure (according to RECIST) and sometimes confirmed by PET. LF and RF were calculated from date of diagnosis until first date of failure, last date of FU or death. OS was calculated from the date of pathologically proven diagnosis until last date of FU or death. Progression-free survival (PFS) was calculated from the date of pathologically proven NSCLC until the date of first failure (local, regional, distant), last date of FU or death. LF, RF and PFS were classified based on FU-records, imaging reports of tumour progression and repeat CT-scans.

Statistical analysis

Patient and tumour characteristics at baseline are presented as the mean (+standard deviation (SD) or the median (+ interquartile range, IQR) and proportions in case of a categorical variable. The independent samples T-test was performed to compare characteristics in case of a normal distribution (age and OAR dose volume parameters). The Mann-Whitney U-test was used to compare continuous variables in non-normal distributions (volume of the primary tumour and lymph nodes). The Pearson's chi-squared test was performed to compare the patient and tumour characteristics as well as the toxicity and failure rates in case of binary, nominal or ordinal variables and a non-normal distribution. Kaplan-Meier survival curves for the reference-cohort and reduction-cohort were plotted for each endpoint. Log-rank tests were performed to assess differences in late toxicity, LF, RF, OS and PFS between the reference-cohort and reduction-cohort. Proportional hazards assumptions for each model were tested by interpretation of the survival plots. Cox proportional hazards analyses were performed to assess the independent effect of dose-reduction on each endpoint. First, a univariate model was constructed. Then, we subsequently adjusted for possible confounding or mediating variables. The variables included are known to be associated with dose-reduction and/or are closely related to outcome. To assess improvement of the model, percentage changes in the HR ≥10% were tested [20]. Since the toxicity profile of cCRT is different compared to sCRT and RT-only (sCRT/RT), a subgroup analysis was performed between cCRT and sCRT/RT [21]. P-values <0.05 were considered statistically significant. The data were analysed using SPSS software, version 25.0, for Windows (IBM).

Results

A total of 308 consecutive patients were included in this study with 170 patients in the reference-cohort and 138 patients in the reduction-cohort. The majority of the patients (70%) received cCRT in both cohorts. The median follow-up time was: 49 months (IQR 39-53) 48 months (IQR 42-57) for the reference-cohort and 21 months (IQR 15-27) 27 months (IQR 22-34) for the reduction-cohort, respectively. Twenty patients were excluded: 3 patients who received 60 Gy ($EQD2_{10}$) before June 2015 due to a high MLD (>20 Gy) and 17 patients who received 70 Gy ($EQD2_{10}$) to the mediastinum after June 2015. The reasons were: individually decided by clinician (n=5), inclusion of the hilar nodes within the primary tumour volume (n=7), by mistake (n=4) or treated within a study protocol (n=1). Patient and tumour characteristics are shown in **Table 1**; no significant differences were observed between the 2 cohorts, except T-stage: the patients with T0-X and T3 were unevenly distributed favouring the reference-cohort. However, the volume of the primary tumour was comparable. For both cohorts, the median GTV of the primary tumour was three-times larger than the GTV of the involved lymph nodes. The median radiation doses to the OAR are shown in **Table 2**.

Table 1: Baseline patient and tumour characteristics in relative numbers (absolute numbers between brackets).

Characteristic	Reference (N=170)	Reduction (N=138)	Total N=308	P-value
Median age (IQR)	65 (59-72)	65 (59-70)	65 (59-71)	0.192
Gender				0.188
Male	58.2% (99)	50.7% (70)	54.9% (169)	
Female	41.8% (71)	49.3% (68)	45.1% (139)	
Performance status				0.584
WHO 0	38.8% (66)	34.1% (47)	36.7% (113)	
WHO 1	53.5% (91)	59.4% (82)	56.2% (173)	
WHO 2	7.6% (13)	6.5% (9)	7.1% (22)	
T-stage				0.008
T0-X	7.6% (13)	1.4% (2)	4.9% (15)	0.012
T1	15.9% (27)	16.7% (23)	16.2% (50)	0.853
T2	27.1% (46)	24.6% (34)	26.0% (80)	0.630
T3	12.9% (22)	26.1% (36)	18.8% (58)	0.003
T4	36.5% (62)	31.2% (43)	34.1% (105)	0.337

Characteristic	Reference (N=170)	Reduction (N=138)	Total N=308	P-value
N-stage				0.284
N1	10.0% (17)	14.5% (20)	37 (12.0%)	
N2	71.2% (121)	63.0% (87)	67.5% (208)	
N3	18.8% (32)	22.5% (31)	20.5% (63)	
TNM-stage (%)				0.345
IIB	5.3% (9)	3.6% (5)	4.5% (14)	
IIIA	38.8% (66)	40.6% (56)	39.6% (122)	
IIIB	47.1% (80)	41.3% (57)	44.5% (137)	
IIIC	8.2% (14)	11.6% (16)	9.7% (30)	
IVa	0.6% (1)	2.9% (4)	1.6% (5)	
Histology (%)				0.873
Adenocarcinoma	42.4% (72)	44.2% (61)	43.2% (133)	
Squamous cell	37.6% (64)	34.8% (48)	36.4% (112)	
Not otherwise specified	20.0% (34)	21.0% (29)	20.5% (63)	
Chemotherapy				0.420
Concurrent	68.2% (116)	72.5% (100)	70.1% (216)	
Sequential + RT alone	31.8% (54)	27.5% (38)	29.9% (92)	
Median GTV (cc) (IQR)				
Primary tumour	51.9 (10.7-117.2)	52.2 (13.1-119.7)	51.9 (12.6-118.5)	0.891
Lymph nodes	15.9 (6.5-39.2)	16.8 (8.0-38.3)	16.3 (7.1-38.7)	0.475
Tumour and nodes	83.6 (46.1-170.0)	87.0 (42.0-151.8)	85.5 (44.3-158.2)	0.501
Median PTV (cc) (IQR)				
Primary tumour	332.5 (123.9-457.6)	252.4 (78.6-378.1)	298.8 (87.9-411.5)	0.013
Lymph nodes	192.1 (84.5-270.5)	155.1 (66.7-201.7)	175.0 (77.0-245.9)	0.035
Tumour and nodes	471.7 (278.0-592.8)	393.0 (244.5-510.6)	437.9 (256.3-551.2)	0.031

GTV = gross tumour volume; PTV = planning target volumes; IQR = interquartile range; RT = radiotherapy

Table 2: The mean dose and standard deviation (SD) of the organs at risk stratified for the reference-cohort and reduction-cohort.

Organ at risk		Reference (N=170) (Mean, SD)	Reduction (N=138) (Mean, SD)	P-value
Heart	V_2 (%)	53.8 (25.9)	51.7 (27.4)	0.491
	Mean (Gy)	13.8 (7.9)	12.0 (6.6)	0.030
Oesophagus	V_{50} (%)	27.6 (16.2)	20.8 (16.0)	<0.001
Lung	V_5 (%)	59.6 (13.9)	58.5 (14.9)	0.147
	MLD (Gy)	14.3 (3.4)	13.0 (3.2)	0.001
Spinal cord	D_{max} (Gy)	41.6 (7.9)	37.7 (9.9)	<0.001

All doses are normalized total dose (EQD2) for spinal cord and plexus α/β=2 Gy; for lungs, heart and mediastinal envelope α/β=3 Gy and for the oesophagus α/β=10 Gy. SD = standard deviation; Heart V2=volume of the heart receiving ≥2 Gy; Oesophagus V50=volume of the oesophagus receiving ≥50 Gy (EQD210); Lung V5=volume of the lungs receiving ≥5 Gy; MLD=mean lung dose; Spinal cord Dmax=maximum dose to 0.1cc of the volume.L

The overall ≥ grade 2 (G2) acute toxicity rates were significantly lower in the reduction-cohort (**Table 3A**). G2 and G3 pulmonary toxicity, consisting of cough, dyspnea and radiation pneumonitis, was significantly lower in the reduction-cohort (20.6% versus 4.3%; 1.8% versus 0.0%). G2 and G3 dysphagia was also significantly lower in the reduction-cohort: 48.2% vs. 37.0% and 12.9% versus 3.6%, respectively. However, the reduction in dose and margins did not result in a decreased late toxicity (**Table 3B**). Late toxicity rates were comparable between the 2 cohorts, except G2 cough (7.1% versus 1.4%). An additional comparison between the 2 cohorts treated with cCRT or sCRT/RT regarding the acute toxicity rates showed significant differences of dysphagia and cough (supplemental **Table S1a-b**). This demonstrated the beneficial effect of the reduction-cohort independent of chemoradiotherapy-schedule. In total, 13 patients (4.2%) died due to a G5 adverse event. In 5 patients, an acute G5 toxicity was reported, all were treated in the reference-cohort: 1 (0.6%) patient died due to a pulmonary haemorrhage and 4 (2.4%) patients died because of pneumonitis. Eight patients died due to a possible G5 late toxicity, of which 5 patients (2.9%) were treated in the reference-cohort: an oesophageal fistula (n=1), a pulmonary haemorrhage (n=1), pneumonitis (n=3) and respiratory insufficiency (n=1). In the reduction-cohort, 3 patients (2.2%) died due to a possible G5: a fatal haemorrhage (n=1) and radiation pneumonitis (n=2). The proportion of patients that died due to an acute G5 adverse event was lower in the reduction-cohort (p=0.042), however, the incidence of late G5 adverse events did not differ (p=0.668).

The LF and RF rates were not significantly different (**Table 4 and Fig. 1a-b**). The median PFS was not significantly different as well (supplementary material, **Fig. S1b**). However, a significant difference was found between the OS of the 2 cohorts (P=0.006, HR 0.63, 95%CI 0.45-0.88; Fig 1C). The median OS was 26 months (IQR 11-56) for the reference-cohort versus 35 months (IQR 19 – N.A.) for the reduction-cohort, respectively. The 1-, 2- and 3- year OS was 70.6%, 51.8% and 38.1% for the reference-cohort and 87.6%, 66.8% and 49.4% for the reduction-cohort, respectively. **Table 5** represents a Cox proportional hazards model for OS in the reduction-cohort. MLD and pulmonary toxicity influenced the association to some extent, but not entirely. No differences were found in the association between the reduction-cohort and OS for cCRT or sCRT/RT (HR 0.67; HR 0.83).

Table 3a: The acute toxicity, scored according to the CTCAE, represented in relative and absolute numbers, as well as the maximum grade of toxicity. Separately reported for the reference-cohort (N=170) and the reduction-cohort (N=138).

Adverse event	G2		G3		G4		G5		P-value (≥G2)
	Reference	Reduction	Reference	Reduction	Reference	Reduction	Reference	Reduction	
Fatigue	6.5% (11)	7.2% (10)	-	-	-	-	-	-	0.788
Anorexia	12.4% (21)	3.6% (5)	11.2% (19)	-	-	-	-	-	<0.001
Dysphagia	48.2% (82)	37.0% (51)	12.9% (22)	3.6% (5)	-	-	-	-	0.001
Cough	11.8% (20)	1.4% (2)	-	-	-	-	-	-	0.001
Dyspnea	8.2% (14)	1.4% (2)	0.6% (1)	-	-	-	2.4% (4)	-	0.009
Radiation pneumonitis	6.5% (11)	1.4% (2)	1.8% (3)	-	-	-	2.4% (4)	-	0.012
Pulmonary toxicity	20.6% (35)	4.3% (6)	1.8% (3)	-	-	-	2.4% (4)	-	<0.001
Hemoptoe	1.2% (2)	-	-	-	-		0.6% (1)	-	0.292
Total number of patients	58.8% (100)	50.7% (70)	15.9% (27)	5.1% (7)	-	-	2.9% (5)	-	<0.001

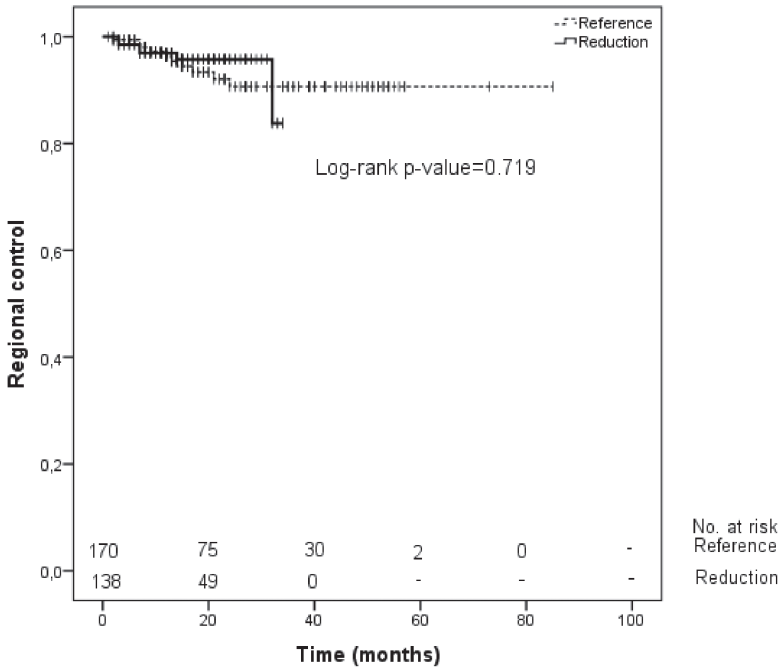
Table 3b: The late toxicity, scored according to the CTCAE, represented in relative and absolute numbers, as well as the maximum grade of toxicity. Separately reported for the Reference-cohort (N=170) and the Reduction-cohort (N=138).

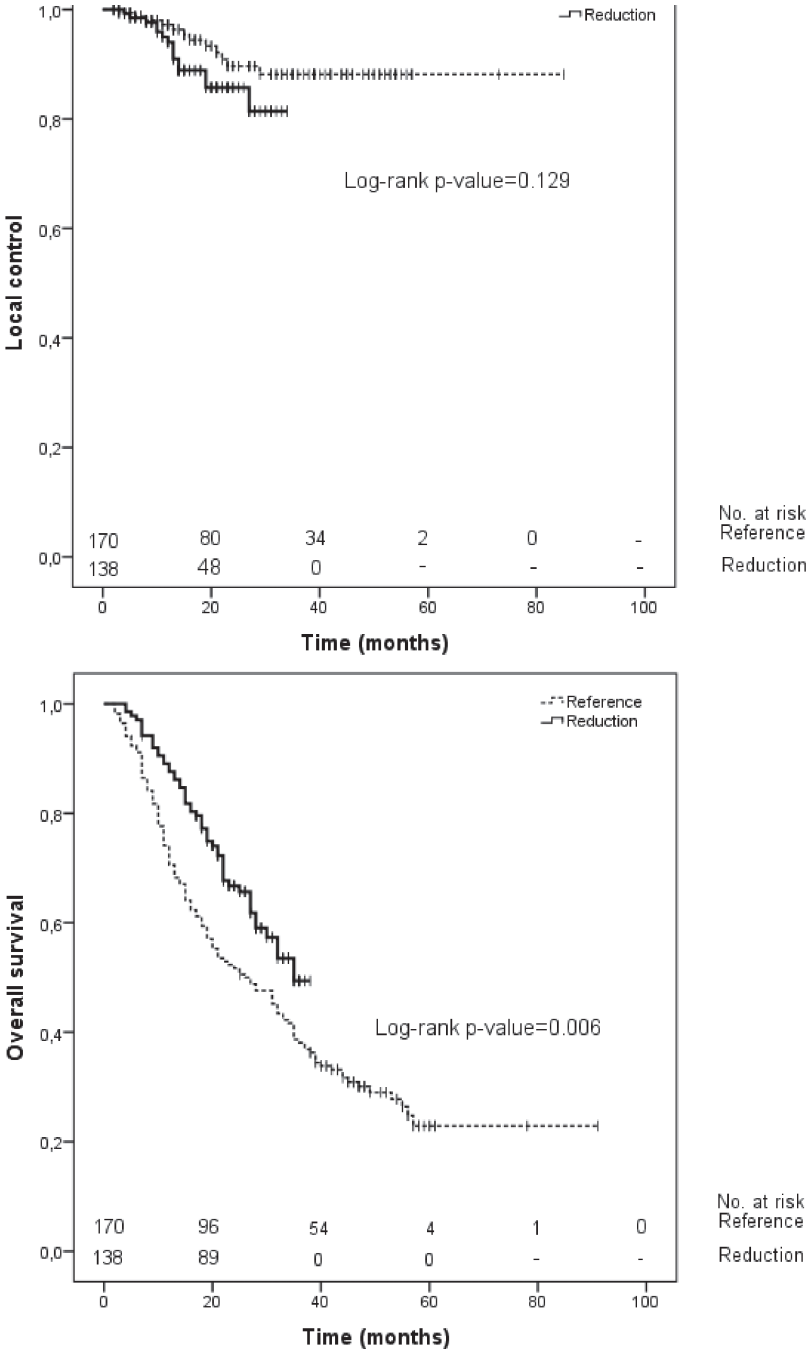
Adverse event	G2		G3		G4		G5		P-value (≥G2)
	Reference	Reduction	Reference	Reduction	Reference	Reduction	Reference	Reduction	
Fatigue	3.0% (5)	1.4% (2)	1.2% (2)	-	-	-	-	-	0.294
Dysphagia	4.7% (8)	0.7% (1)	3.0% (5)	0.7% (1)	-	-	0.6% (1)	-	0.063
Cough	7.1% (12)	1.4% (2)	-	-	-	-	-	-	0.018
Dyspnea	5.9% (10)	5.8% (8)	2.4% (4)	1.4% (2)	-	0.7% (1)	1.8% (3)	0.7% (1)	0.697
Radiation pneumonitis	15.3% (26)	10.9 (15)	3.5% (6)	1.4% (2)	0.6% (1)	-	1.8% (3)	1.4% (2)	0.428
Pulmonary hemorrhage	1.2% (2)	-	0.6% (1)	-	-	-	0.6% (1)	0.7% (1)	0.477
Vertebral fracture	2.4% (4)	-	1.2% (2)	-	-	-	-	-	0.082
Brachial plexopathy	0.6% (1)	-	-	-	-	-	-	-	0.365
Chest wall pain	2.4% (4)	2.2% (3)	-	-	-	-	-	-	0.910
Total number of patients	25.9% (44)	19.6% (27)	7.6% (13)	2.2% (3)	0.6% (1)	0.7% (1)	2.9% (5)	2.2% (3)	0.110

Table 4: Local and regional failures (crude incidence and the 1- and 2-year rates) in relative and absolute number of the 308 patients for the 2 cohorts receiving 70 Gy (N=170) and 60 Gy (N=138) to the involved lymph nodes, while prescribing the tumor 70 Gy ($EQD2_{10}$).

Failures	Reference	Reduction	Total	P
LF only	7.1% (12)	10.9% (15)	8.8% (27)	0.129
RF only	5.9% (10)	4.3% (6)	5.2% (16)	0.719
Both LF and RF	7.1% (12)	3.6% (5)	5.5% (17)	0.375
Outfield RF only	1.8% (3)	2.9% (4)	2.3% (7)	0.146
LF rate				
1-year	5.4%	8.3%		
2-year	18.2%	18.6%		
RF rate				
1-year	8.0%	5.6%		
2-year	16.4%	9.2%		

LF: local failure; RF: regional failure.





▲**Figure 1:**Kaplan-Meier curves of the regional control (a), local control (b) and overall survival (c) compared between the reference-cohort (N = 170) and the reduction-cohort (N = 138)

Table 5: Association Cox proportional hazards analysis to test the association for overall survival between the reduction-cohort and patient, tumour, treatment characteristics and toxicity.

	HR (95% CI)	P	Relative HR change
Reduction	0.63 (0.45, 0.88)	0.007	-
+ MLD	0.70 (0.50, 0.98)	0.039	11.1%
+ Heart V_2	0.61 (0.43, 0.86)	0.004	3.2%
+ Mean heart dose	0.64 (0.45, 0.90)	0.011	1.6%
+ Oesophagus V_{50}	0.67 (0.48, 0.94)	0.021	6.3%
+ Acute toxicity ≥G3	0.67 (0.47, 0.94)	0.019	6.3%
+ Acute pulmonary toxicity ≥G3	0.68 (0.48, 0.95)	0.024	7.9%
+ Acute dysphagia ≥G3	0.63 (0.45, 0.89)	0.008	-
+ Late toxicity ≥G3	0.64 (0.46, 0.90)	0.010	1.6%
+ Late pulmonary toxicity ≥G3	0.64 (0.46, 0.89)	0.009	1.6%
+ Late dysphagia ≥G3	0.62 (0.44, 0.87)	0.005	1.6%

MLD=mean lung dose; Heart V2=volume of the heart receiving ≥2 Gy; Oesophagus V50 =volume of the oesophagus receiving ≥50 Gy (EQD210); Pulmonary toxicity=cough, dyspnea and radiation pneumonitis.

Discussion

Previously, we published the results of a differential analysis of local and regional control after chemoradiotherapy, demonstrating that lymph nodes recur less often than the primary tumor due to a lower volume [12]. The current analysis in LA-NSCLC patients compared 70 Gy ($EQD2_{10}$) versus 60 Gy ($EQD2_{10}$) to the mediastinal lymph nodes while treating the primary tumour to 70 Gy ($EQD2_{10}$) using IMRT. Simultaneously, the PTV-margins were reduced following the implementation of daily image guidance with online carina registration replacing a bony anatomy registration. Comparison with a historical cohort, treated with 70 Gy ($EQD2_{10}$) to both the primary tumour and the lymph nodes, was performed to determine the safety of this new treatment strategy in terms of toxicity and RF. The reduction-cohort demonstrated significantly lower acute toxicity rates, a comparable incidence of LF and RF as well as a significantly improved OS.

Since the RTOG-0617, dose-escalation while increasing the overall treatment time in lung cancer, is regarded with restraint. This phase 3-trial reported an increased acute toxicity as well as a worse OS in the conventionally fractionated 74 Gy-arm compared to the 60 Gy-arm of 20.3 vs 28.7 months, respectively, in patients treated with concurrent chemotherapy (weekly Paclitaxel and Carboplatin +/- Cetuximab) [1].

Heart dose parameters (V_5 and V_{30}) and the presence of dysphagia were associated with OS. In addition to the RTOG-0617, Hallqvist et al. recently published their toxicity results of a randomized phase II-trial [22]. Thirty-six patients were treated with an escalated dose up to 84 Gy to the tumour and involved mediastinum concurrently with 3-weekly Cisplatin-Vinorelbin. Seven patients died due to a possible G5 toxicity (pneumonitis and oesophageal fistulae) of which 5 patients were included in the 84 Gy-arm. The study was stopped after this pre-planned safety analysis. The conclusion of the RTOG-0617 and the Hallqvist-trial was that the acute and late toxicities were at least partly responsible for the negative results. It should be emphasized that the primary tumour as well as the involved lymph nodes were exposed to the escalated dose. In the current study, we reduced the total dose to the mediastinum, but not the primary tumour. Combining a lower mediastinal dose with a reduction of the PTV-margins resulted in a significantly lower exposure of the OAR (Table 2), a significantly lower incidence of severe ≥G3 acute dysphagia and acute pulmonary toxicity as well as an improved OS.

The lower toxicity rates favoured the reduction-cohort, but the safety of this regimen also depends on the RF rate. No increase in RF with or without LF was observed (**Table 4**). A previously published study by Van den Bosch et al. supported our results by demonstrating that an increased RT dose was not associated with a lower RF rate [23]. Seventy-five stage IIB-IV NSCLC patients were treated with a dose between 42-66 Gy ($EQD2_{10}$) to the tumour as well as the lymph nodes, of which 63% received sCRT. The RF rate was not different between lower and higher radiation dose to involved lymph nodes and varied between 6-8%. However, the primary tumour did show a dose-effect relationship. Several papers showed similar results, although the RTOG-0617 did not reveal lower LF rates [1, 13]. In addition to the already mentioned potential causes of the detrimental outcome of the 74Gy-arm, the extended overall treatment time probably resulted in reduced effectiveness. This disadvantage may be countered by hypofractionated RT with a positive effect on OS [3, 24]. However, the hypofractionated schedule used in the current analysis differs from the conventionally fractionated schedule and could potentially increase the toxicity. Since the introduction of our hypofractionated schedule, after being tested within a phase II and III EORTC-trial, we have monitored the toxicity closely and published about the acute and long term outcome [25-28]. The acute and late toxicity rates are favorable compared to the toxicity of the conventional fractionated schedules with full dose chemotherapy [1].

The patients treated in the reduction-cohort revealed a better median OS than the reference-cohort. It is unclear whether there is an independent association between dose-reduction and OS. MLD was found to influence the association between dose-reduction and OS. However, the reduced dose to the mediastinum could potentially have the greatest impact, which might also explain the negative outcome of the RTOG-0617. The great advantage of a differential dose-prescription to the primary tumour and involved lymph nodes is the balance between maximizing the local control (high dose to the primary tumour) while the toxicity rates decrease because of a less intense dose to the mediastinum. Due to this favourable profile many patients, including the elderly and the patients with considerable co-morbidity, can benefit from this intensive treatment with curative intent.

We acknowledge that the observational nature of this study has its limitations. First, this is a retrospective analysis. Second, since heart toxicity is insufficiently recognized during FU, we were not able to report on the acute and late heart toxicity in detail. Third, the median FU differed between the 2 cohorts. Nevertheless, with a median FU of 27 months in the reduction-cohort, we are confident that the majority of the local and regional failures have developed already. Also, to compare the two cohorts with a similar FU, we censored the reference-cohort after 27 months. No different outcomes were observed (supplementary material, **Fig.S2a-c**). Fourth, 17 patients who received 70 Gy ($EQD2_{10}$) to the mediastinum due to a protocol violation and were excluded. The median OS between these 17 patients and the reduction-cohort was comparable; therefore we believe that excluding these patients did not influence outcome. Last, we simultaneously implemented 2 treatment adaptations resulting in a lower dose to the OARs followed by a decrease in the acute toxicity rates. To distinguish the contribution of each adaptation is challenging. We have calculated within a subset of the patients the effect of the reduced margins as well as the dose reduction to the lymph nodes on the MLD and other dose parameters (supplementary material, **Table S3A-C**).

In conclusion, this observational study compared dose-reduction to the lymph nodes as well as a margin reduction in 2 consecutive LA-NSCLC cohorts +/- concurrent or sequential chemotherapy. With 60 Gy ($EQD2_{10}$) instead of 70 Gy ($EQD2_{10}$) to the involved mediastinal lymph nodes of LA-NSCLC patients, the acute toxicity rates decreased significantly while the RF rates were comparable. Furthermore, OS improved significantly. A differentiated dose to primary tumour and lymph nodes

using a hypofractionated regimen is a safe treatment strategy with very low toxicity for LA-NSCLC patients.

Acknowledgement

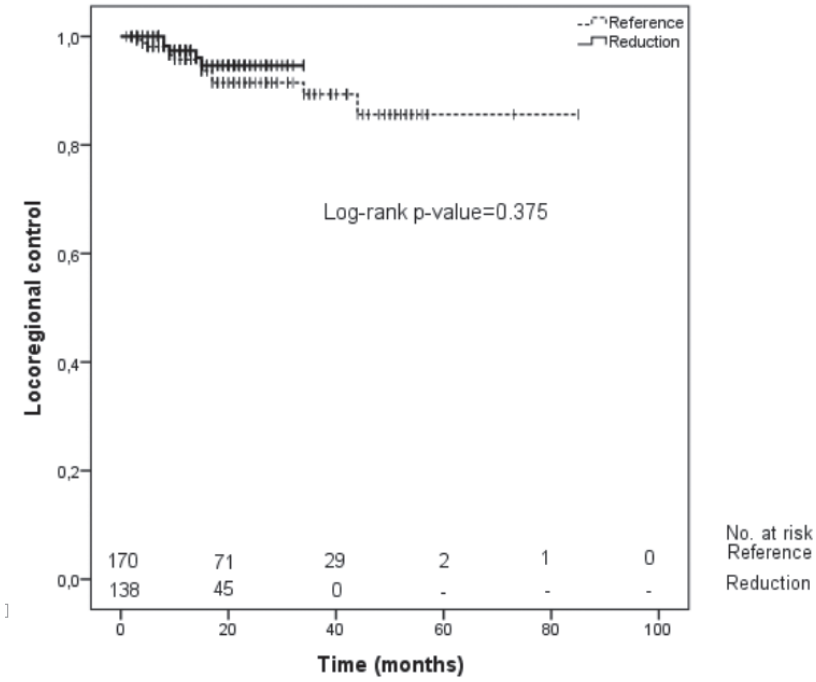
The authors acknowledge Tomas Janssen for providing the tumour volumes.

References

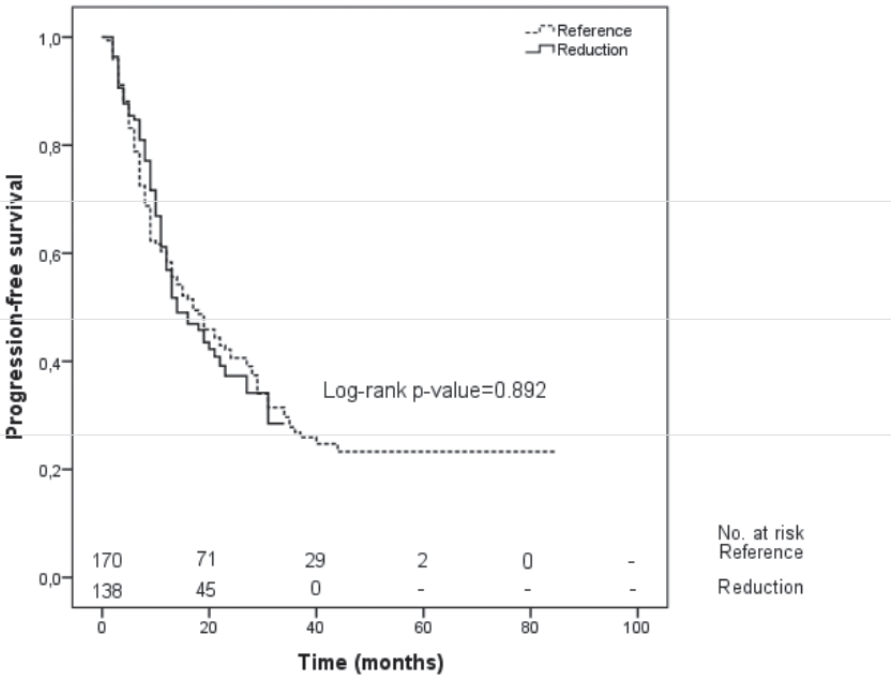
1. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16:187-99.
2. Bradley JD, Hu C, Komaki RU, Masters G, Blumenschein GR, Schild SE, et al. Long-Term Results of RTOG 0617: A Randomized Phase 3 Comparison of Standard Dose Versus High Dose Conformal Chemoradiation Therapy +/- Cetuximab for Stage III NSCLC. International Journal of Radiation Oncology • Biology • Physics. 2017;99:S105.
3. Kaster TS, Yaremko B, Palma DA, Rodrigues GB. Radical-intent hypofractionated radiotherapy for locally advanced non-small-cell lung cancer: a systematic review of the literature. Clin Lung Cancer. 2015;16:71-9.
4. Koning CC, Wouterse SJ, Daams JG, Uitterhoeve LL, van den Heuvel MM, Belderbos JS. Toxicity of concurrent radiochemotherapy for locally advanced non--small-cell lung cancer: a systematic review of the literature. Clin Lung Cancer. 2013;14:481-7.
5. Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys. 2010;76:S86-93.
6. [6] Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys. 2010;76:S70-6.
7. Tucker SL, Liu A, Gomez D, Tang LL, Allen P, Yang J, et al. Impact of heart and lung dose on early survival in patients with non-small cell lung cancer treated with chemoradiation. Radiother Oncol. 2016;119:495-500.
8. Kwint M, Uyterlinde W, Nijkamp J, Chen C, de Bois J, Sonke JJ, et al. Acute esophagus toxicity in lung cancer patients after intensity modulated radiation therapy and concurrent chemotherapy. Int J Radiat Oncol Biol Phys. 2012;84:e223-8.
9. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87:690-6.
10. Stam B, van der Bijl E, van Diessen J, Rossi MMG, Tijhuis A, Belderbos JSA, et al. Heart dose associated with overall survival in locally advanced NSCLC patients treated with hypofractionated chemoradiotherapy. Radiother Oncol. 2017;125:62-5.
11. Ferris MJ, Zhong J, Switchenko JM, Higgins KA, Cassidy RJ, 3rd, McDonald MW, et al. Brainstem dose is associated with patient-reported acute fatigue in head and neck cancer radiation therapy. Radiother Oncol. 2018;126:100-6.
12. van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential analysis of local and regional failure in locally advanced non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Radiother Oncol. 2016;118:447-52.
13. Schytte T, Nielsen TB, Brink C, Hansen O. Pattern of loco-regional failure after definitive radiotherapy for non-small cell lung cancer. Acta Oncol. 2014;53:336-41.
14. Jouglar E, Isnardi V, Goulon D, Segura-Ferlay C, Ayadi M, Dupuy C, et al. Patterns of locoregional failure in locally advanced non-small cell lung cancer treated with definitive conformal radiotherapy: Results from the Gating 2006 trial. Radiother Oncol. 2018;126:291-9.

15. Schaake EE, Rossi MM, Buikhuisen WA, Burgers JA, Smit AA, Belderbos JS, et al. Differential motion between mediastinal lymph nodes and primary tumor in radically irradiated lung cancer patients. Int J Radiat Oncol Biol Phys. 2014;90:959-66.
16. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging. 2008;35:2320-33.
17. Wolthaus JW, Schneider C, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys. 2006;65:1560-71.
18. van Herk M, Remeijer P, Lebesque JV. Inclusion of geometric uncertainties in treatment plan evaluation. Int J Radiat Oncol Biol Phys. 2002;52:1407-22.
19. Kwint M, Conijn S, Schaake E, Knegjens J, Rossi M, Remeijer P, et al. Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy. Radiother Oncol. 2014;113:392-7.
20. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138:923-36.
21. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010:CD002140.
22. Hallqvist A, Bergstrom S, Bjorkestrand H, Svard AM, Ekman S, Lundin E, et al. Dose escalation to 84 Gy with concurrent chemotherapy in stage III NSCLC appears excessively toxic: Results from a prematurely terminated randomized phase II trial. Lung Cancer. 2018;122:180-6.
23. Agrawal V, Coroller TP, Hou Y, Lee SW, Romano JL, Baldini EH, et al. Lymph node volume predicts survival but not nodal clearance in Stage IIIA-IIIB NSCLC. PLoS One. 2017;12:e0174268.
24. Walraven I, van den Heuvel M, van Diessen J, Schaake E, Uyterlinde W, Aerts J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Radiother Oncol. 2016;118:442-6.
25. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). Eur J Cancer. 2007;43:114-21.
26. Uyterlinde W, Belderbos J, Baas C, van Werkhoven E, Knegjens J, Baas P, et al. Prediction of acute toxicity grade >/= 3 in patients with locally advanced non-small-cell lung cancer receiving intensity modulated radiotherapy and concurrent low-dose Cisplatin. Clin Lung Cancer. 2013;14:541-8.
27. Chen C, Uyterlinde W, Sonke JJ, de Bois J, van den Heuvel M, Belderbos J. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. Radiother Oncol. 2013;108:337-41.
28. Dieleman EMT, Uitterhoeve ALJ, van Hoek MW, van Os RM, Wiersma J, Koolen MGJ, et al. Concurrent Daily Cisplatin and High-Dose Radiation Therapy in Patients With Stage III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2018;102:543-51.

Supplementary material



▲**Figure S1a:** Kaplan-Meier curves of the locoregional control rate compared between the reference-cohort (N=170) and the reduction-cohort (N=138).



▲**Figure S1b:** Kaplan-Meier curves of the progression-free survival compared between the reference-cohort (N=170) and the reduction-cohort (N=138).

Table S2.: Univariate Cox proportional hazards analysis for overall survival.

	HR (95% CI)	P
Reduction	0.63 (0.45, 0.88)	0.007
MLD	1.11 (1.06, 1.16)	<0.001
Heart V_2	1.01 (1.00, 1.01)	0.002
Mean heart dose	1.04 (1.02, 1.06)	<0.001
Oesophagus V_{50}	1.01 (1.00, 1.02)	0.016
Acute toxicity ≥G3	1.60 (1.08, 2.37)	0.019
Acute pulmonary toxicity ≥G3	10.03 (4.60, 21.88)	<0.001
Acute dysphagia ≥G3	1.10 (0.68, 1.80)	0.694
Late toxicity ≥G3	1.32 (0.84, 2.10)	0.223
Late pulmonary toxicity ≥G3	1.78 (1.06, 2.98)	0.026
Late dysphagia ≥G3	0.83 (0.34, 2.02)	0.681

MLD=mean lung dose; Heart V2=volume of the heart receiving ≥2 Gy; Oesophagus V50 =volume of the heart receiving ≥50 Gy (EQD210); Pulmonary toxicity=cough, dyspnea and radiation pneumonitis.

Table S3A-C. The dose to the organs at risk specified to 4 different radiotherapy conditions (A-D) of the involved lymph nodes in 10 patients to gain more insight in the toxicity profile of the reduction of the mediastinal dose and the margins, separately. A and D are the conditions of the reference-cohort and the reduction-cohort, respectively. The difference of the mean (Δ Mean) between A and the three other conditions are specified as well as the standard deviation (SD). Comparing margin reduction (B) and dose reduction (C) indicates that the contribution of these strategies for the mean lung dose and mean heart dose to the overall exposure reduction is comparable, while for the V_{50} of the esophagus the contribution of C dominates over the contribution of B.

A=Dose of 70 Gy (EQD_2) and margins using a bone anatomy based correction strategy.

B= Dose of 70 Gy (EQD_2) and margins using a carina based correction strategy.

C= Dose of 60 Gy (EQD_2) and margins using a bone anatomy based correction strategy.

D= Dose of 60 Gy (EQD_2) and margins using a carina based correction strategy.

Table S3A. Mean Lung Dose (Gy)

	1	2	3	4	5	6	7	8	9	10	Δ Mean	SD
A	15.8	19.2	12.3	12.2	16.8	12.2	11.6	10.5	14.3	18.7		
B	15.5	19.0	11.7	12.3	16.1	11.5	11.2	10.4	13.5	16.4	0.6	0.63
C	14.7	17	11.5	12.1	15.2	11.4	10.8	9.6	13.6	17.5	1.0	0.54
D	13.9	15.5	10.7	11.8	14.9	11.2	10.6	9.2	12.9	14.2	1.9	1.21

Table S3B. Mean Heart Dose (Gy)

	1	2	3	4	5	6	7	8	9	10	Δ Mean	SD
A	10.2	9.3	4.0	1.5	11.7	14.8	5.7	2.5	3.8	10.4		
B	8.1	8.8	3.6	1.5	11.3	13.6	5.5	2.6	3.9	9.7	0.5	0.65
C	9.2	9.1	3.3	1.8	11.1	12.4	5.0	2.4	4.0	9.6	0.6	0.73
D	8.7	8.3	3.6	1.9	11.2	12.2	5.2	2.5	4.2	8.4	0.8	0.95

Table S3C. The volume of the oesophagus receiving ≥50 Gy (%)

	1	2	3	4	5	6	7	8	9	10	Δ Mean	SD
A	18.9	30.8	8	0	29.6	32.3	22.3	10.4	40.3	18.4		
B	17.6	30.5	8.4	0	25.7	32.2	21.3	10.3	37.7	16.6	1.1	1.3
C	15.7	26.1	5.2	0.9	13.3	31.0	18.9	5.2	36.8	14.9	4.3	4.3
D	13.9	23.0	1.0	1.2	10.0	31.3	17.5	2.2	36.1	11.2	6.4	5.3

CHAPTER 3

OUTCOME OF RADICAL LOCAL TREATMENT OF NON-SMALL CELL LUNG CANCER PATIENTS WITH SYNCHRONOUS OLIGOMETASTASES

Margriet Kwint, Iris Walraven, Sjaak Burgers, Koen Hartemink, Houke Klomp, Joost Knegjens, Marcel Verheij, José Belderbos

Lung Cancer. 2017;112:134-139. doi:10.1016/j.lungcan.2017.08.006

Objectives

Patients with stage IV non-small cell lung cancer (NSCLC) are considered incurable and are mainly treated with palliative intent. This patient group has a poor overall survival (OS) and progression free survival (PFS). The purpose of this study was to investigate PFS and OS of NSCLC patients diagnosed with synchronous oligometastatic disease who underwent radical treatment of both intrathoracic disease and metastases.

Materials and methods

Patients with NSCLC and oligometastatic disease at diagnosis, who were treated with radical intent between 2008 and 2016, were included in this observational study. Treatment consisted of systemic treatment and radical radiotherapy or resection of the intrathoracic disease. Treatment of the metastases consisted of radical or stereotactic radiotherapy, surgical resection or radiofrequency ablation.

Results

Ninety-one patients (52% men, mean age 60 years) in good performance status were included. Thirty-eight patients (42%) died during follow-up (median follow-up 35 months). The cause of dead was lung cancer in all patients, except one. Sixty-three (69%) patients developed recurrent disease. Eleven recurrences (17%) occurred within the irradiated area. For the whole group, the median PFS was 14 months (range 2-89, 95%CI 12-16) and the median OS was 32 months (range 3-89, 95%CI 25-39). The 1- and 2-year OS rates were 85% and 58% and the 1- and 2-year PFS rates were 55% and 27%, respectively.

Conclusions

Radical local treatment of a selected group of NSCLC patients with good performance status presenting with synchronous oligometastatic disease resulted in favorable long-term PFS and OS.

Introduction

Lung cancer is the leading cause of cancer death, with 1.59 million deaths annually worldwide [1]. More than half of the patients with non-small cell lung cancer (NSCLC) are diagnosed with metastatic disease [2].

According to current treatment guidelines, stage IV NSCLC patients are considered incurable and are mainly treated with palliative intent [3]. Nonetheless, the treatment options of stage IV NSCLC patients have increased with a tendency towards a more personalized treatment approach. When a patient has a limited number of metastases (also called 'oligo metastasis' [4,5]), a more radical treatment regime instead of palliative treatment may be beneficial with respect to progression free and/or overall survival [6].

Hellman and Weichselbaum first described the term 'oligometastasis' in 1995 [4,5]. According to this concept, radical/aggressive local cancer treatments might be curative in a proportion of patients with a limited amount of metastases. However, the existing literature is seriously flawed by the lack of a general consensus on the definition of oligometastatic disease. A commonly used definition in the literature is 'metastases limited in number and destination organ'. However, the specific number is not consistently formulated. Often a maximum of 2 metastases are referred to as oligometastatic disease, and treated accordingly [7,8]. In contrast, ≤5 metastases are also mentioned as oligometastatic disease and considered for radical treatment [7] . Considering the lack of a proper definition for oligometastatic disease, there is a need to investigate the association between the number of metastases and survival in stage IV NSCLC patients. Limited retrospective data are available in literature on oligometastatic NSCLC, both on synchronous and metachronous metastases and on heterogeneous treatments including surgery, stereotactic ablative radiotherapy and radical radiotherapy [7-27]. In a recent systematic review on the evidence for the oligometastatic theory in NSCLC, Ashworth et.al. [7] concluded that: "Long-term survivors do exist. Radical treatment of the primary lung tumor and metastases are strongly associated with improved long-term survival". Gomez et.al [14] reported the outcome of a prematurely terminated phase II randomized trial. In this trial, patients with oligometastatic NSCLC without progression after first line systemic therapy were randomized between local consolidative therapy versus maintenance therapy or observation. The outcome showed improved progression free survival for those patients treated with local consolidative therapy.

Hence, radical local treatment on the primary tumor and the metastases seems to improve survival in oligometastatic NSCLC disease [7,8,11,13-15,18-20]. Since a radical treatment approach for synchronous oligometastatic NSCLC is not standard of care according to current treatment guidelines, more evidence is needed to confirm the benefit of this therapeutic approach.

Therefore, the purpose of this observational study was to determine the progression free survival (PFS) and overall survival (OS) of NSCLC patients with good performance, diagnosed with synchronous oligometastatic (<5 metastases) disease treated with curative intent of the intrathoracic disease and the metastases.

Materials and methods

Patients diagnosed with synchronous oligometastatic NSCLC who were treated between July 2008 and August 2016 were included in this observational study. Patients were selected during the multidisciplinary tumor board meeting for thoracic cancer in our institute. When radical local treatment for oligometastatic disease was considered, patients were registered in a database between 2008 and 2016. Details of all patients were retrospectively retrieved using this registration database, with subsequent review of all the patients' charts. Patients who had progressive disease before they finished their radical local treatment were not registered in the database. The Institutional Review Board of our institute waived review because of the retrospective nature of the study.

Inclusion criteria for this analysis included histological or cytological proven NSCLC and less than 5 synchronous metastases at the time of diagnosis. Patients were excluded if they had other uncontrolled malignancies. Staging was done for all patients by fluorodeoxyglucose-positron-emission-tomography-(FDG-PET)-scan, CT-thorax and for the brain a contrast-enhanced magnetic resonance imaging (CE-MRI) or a CT of the brain with intravenous contrast. Ideally, metastatic disease was pathologically proven but this was not mandatory. Different types of local therapies were allowed. Systemic therapy was not mandatory.

For the primary tumor, treatment was considered radical if the patient underwent surgery or if a radical radiotherapy dose was given (≥55 Gy biological equivalent dose (EQD2) / α/ß=10). For the treatment of the metastases, sometimes a lower radiation dose was prescribed (stereotactic radiation for brain metastasis: 1x15 up to 1x24 Gy

(N=25), adrenal gland: 3x8 up to 3x12.5 Gy (N=11), or bone: 3x8 Gy up to 3x15 Gy or 5x7 Gy (N=9)). Other treatment modalities such as radiofrequency ablation (RFA (N=1)) were considered radical as well.

In general, the clinical outcome of the treatment was evaluated 8 weeks after treatment by clinical consultation and repeat CT. Subsequently, follow-up was performed every 3 months by the pulmonologist and radiation oncologist or surgeon. After 2 years, follow-up was performed every 6 months. In case of brain metastases, a MRI-brain was performed every 3 months.

Primary endpoints were progression free survival (PFS) and overall survival (OS). Survival was calculated from date of pathologically proven diagnosis until the last date of follow-up or death. PFS was calculated from date of pathologically proven NSCLC until the date of first progression (local, regional, distant) or death. Progressive disease was scored based on available clinical data or imaging report of tumor progression.

Statistical analysis

Descriptive statistics were used for patient, tumor and treatment characteristics. Median OS and PFS were calculated using the Kaplan-Meier method. Median follow-up was calculated using the reverse Kaplan-Meier method. Univariate Cox regression analysis was done on patient, tumor and treatment characteristics to identify predictors of OS and PFS. P-Values were used to quantify degree of association between each of the factors and the survival-based endpoints. Multivariate Cox regression analysis was performed for OS and PFS, based on selected variables from univariate analysis ($p < 0.10$). Multivariate analysis was done by backward selection, based on p-value with a removal criterion of $p=0.10$. Statistical analysis was carried out by using SPSS (version 22).

Results

Patient selection and treatment variables

Table 1 presents the baseline patient and tumor characteristics. Between July 2008 and August 2016, 91 patients with a mean age of 60 years (range 35-86) were treated and registered in the database and eligible for this analysis. Seventy-seven (85%) patients had a solitary metastasis, 9 (10%) patients had 2 metastases, 2 (2%) patients had 3 metastases and 3 (3%) patients had 4 metastases. The most frequent location

of the metastasis was the brain (42%) followed by bone (30%) and adrenal glands (18%). A mutation analysis was not mandated at the time of diagnosis in our institute. Therefore, Epidermal Growth Factor Receptor (EGFR) was only determined in 57% of the cases. In 11 patients (21%) an EGFR mutation was found. Other mutations were not analyzed since they were reported in a small minority of patients, and no statically power remained to test for this subgroup analysis.

Treatment of the primary tumor consisted of (chemo) radiation (N= 81, 89%) in most patients. The other patients had a surgical intervention (N= 8, 9%) and 2 patients (2%) had no local treatment except systemic therapy. One of these 2 patients had an occult primary tumor and the other patient had a complete response of the primary tumor after targeted therapy.

Seventy-five patients (82%) received systemic treatment (**Table 2**). Nine patients (10%) received concurrent chemo- radiotherapy and 60 patients (66%) received sequential chemo- radiotherapy. Six patients (7%) received targeted therapy.

The fractionation schedule for the radiotherapy was determined by a team of radiation oncologists, with the aim to achieve a radical regime. The most frequently used radiotherapy schedules were 24x2.75 Gy (48%), followed by 17x3 Gy (26%) and in 13% of the patients the primary tumor was treated with an ablative stereotactic radiotherapy schedule. Stereotactic radiotherapy to the lung tumor was chosen if the tumor was located peripheral (< 5 cm) and there were no lymph nodes involved (N0 disease). For 78 patients (86%) who received thoracic radiotherapy for the primary tumor in our institute (3 patients received the radiotherapy in another institute), the mean Gross Tumor Volume (GTV) for the primary tumor was: 71.2 +/- 114, 0 cm^3 (min/max: 0.3 - 741,5 cm^3) (median 28.5 cm^3). The mean total GTV (primary including lymph nodes) was 83.8 +/- 117.8 cm^3 (min/max: 1.4 – 741.5 cm^3) (median 45.8 cm^3). Further treatment characteristics of the treatment of the primary tumor and lymph nodes are shown in **Table 2**.

In 48% of the patients, the metastases were treated with stereotactic radiotherapy. In 22% of the patients the metastases were in close proximity of the primary tumor or pathological lymph nodes and irradiated within the thoracic radiotherapy field (for example a rib metastasis or neck/axillary lymph nodes). Treatment modality for the brain metastases (surgery or stereotactic radiotherapy) was discussed and approved in a neuro-oncology tumor board.

Four out of six patients, who did not receive local therapy for the metastasis, had brain metastases which were considered too small for stereotactic radiotherapy after response to systemic therapy. The other 2 patients (1 liver and 1 bone metastasis) had a complete response after systemic treatment for the metastasis and only received radical treated for the primary tumor. Further treatment characteristics of the treatment of the metastases are shown in **Table 3**.

Table 1: patients and tumor characteristics. WHO = world health organization, NOS: not otherwise specified. TNM 7th edition was used for staging. * within brackets number of metastasis.

Patient and tumor characteristics	**N (%)**
Sex	
Male	48 (52.7%)
Female	43 (47.3%)
WHO performance status	
0	44 (48.4%)
1	45 (49.5%)
2	2 (2.2%)
Stage (ignoring M-status)	
1A	10 (11.0%)
1B	3 (3.3%)
2A	11 (12.1%)
2B	10 (11.0%)
3A	33 (36.3%)
3B	24 (26.4%)
T-stage	
T0-Tx	2 (2.2%)
T1	24 (26.4%)
T2	33 (36.3%)
T3	14 (15.4%)
T4	18 (19.8%)
Nodal stage	
N0	32 (35.2%)
N1	10 (11.0%)
N2	33 (36.3%)
N3	16 (17.6%)
Pathology	
Adenocarcinoma	58 (63.7%)
Squamouscellcarcinoma	9 (9.9%)
Large cell neuro-endocrine carcinoma	6 (6.6%)
Non-small-cell lung cancer NOS	18 (19.8%)
Number metastases	
1	77 (84.6%)
2	9 (9.9%)
3	2 (2.2%)
4	3 (3.3%)

Patient and tumor characteristics	**N (%)**
Location metastases	
Brain (1)*	29 (31.9%)
Brain (2)	3 (3.3%)
Brain (3)	1 (1.1%)
Brain (4)	3 (3.3%)
Bone	23 (25.3%)
Bone (2)	1 (1.1%)
Adrenal gland	13 (14.3%)
Lymph node	6 (6.6%)
Liver	2 (2.2%)
Soft tissue	1 (1.1%)
Pulmonary	1 (1.1%)
Thyroid Gland	1 (1.1%)
Breast	1 (1.1%)
Liver and bone	1 (1.1%)
Pleural and bone	1 (1.1%)
Brain and bone	1 (1.1%)
Adrenal gland and pulmonary	1 (1.1%)
Adrenal gland and brain	1 (1.1%)
Adrenal gland (2) and lymph node	1(1.1%)

Table 2: treatment characteristics of the primary tumor and lymph nodes. RT= Radiotherapy, * 1 patient with an occult primary tumor and 1 patient with complete response after targeted therapy of the primary tumor.

Treatment primary tumor and lymph nodes	N (%)
Local treatment	
Radiotherapy	81 (89.0%)
Radiotherapy only conventional RT	*3*
Radiotherapy only stereotactic RT	*7*
Sequential + conventional RT	*56*
Sequential + stereotactic RT	*4*
Concurrent fulldose +conventional RT	*3*
Concurrent lowdose + conventional RT	*6*
Targeted therapy + conventional RT	*1*
Targeted therapy + stereotactic RT	*1*
Surgery	8 (8.8%)
Lobectomy	*5*
Segment resection	*1*
Sequential chemo + lobectomy	*2*
Systemic only*	2 (2.2%)
Targeted therapy	*1*
Chemotherapy	*1*

Type Systemic Therapy	
None	*16 (17.6%)*
Daily lowdose Cisplatin (Concurrent)	*6 (6.6%)*
Cisplatin-Etoposide (Concurrent)	*2 (2.2%)*
Cisplatin-Pemetrexed (Concurrent)	*1 (1.1%)*
Cisplatin-Pemetrexed	*26(28.6%)*
Cisplatin-Gemcitabine	*12 (13.2%)*
Cisplatin-Etoposide	*2 (2.2%)*
Cisplatin-Pemtrexed+ Pemetrexed maintenance	*2 (2.2%)*
Cisplatin/Carboplatin-Gemcitabine	*2 (2.2%)*
Carboplatin-Gemcitabine	*7 (7.7%)*
Carboplatin-Pemetrexed	*9 (9.9%)*
Tarceva	*2 (2.2%)*
Gefitinib	*4 (4.4%)*

Table 3: treatment characteristics of the metastases. RT= Radiotherapy, RFA = Radio Frequency Ablation

Treatment of the metastases	**N (%)**
Stereotactic Radiotherapy	44 (48.4%)
Brain	*24*
Adrenal gland	*10*
Bone	*8*
Brain & bone	*1*
Brain & adrenal gland	*1*
Conventional radiotherapy within thoracic RT-field	20 (22.0%)
Bone	12
Lymph node	*4*
Soft Tissue	*1*
Pulmonary	*1*
Thyroid gland	*1*
Bone & Pleura	*1*
Conventional radiotherapy	7 (7.7%)
Bone	*3*
Lymph node	*2*
Liver	*1*
breast	*1*
Systemic therapy only	6 (6.6%)
brain	*4*
Adrenal gland	*1*
Liver & bone	*1*
Surgery and radiotherapy	6 (6.6%)
Brain	*4*

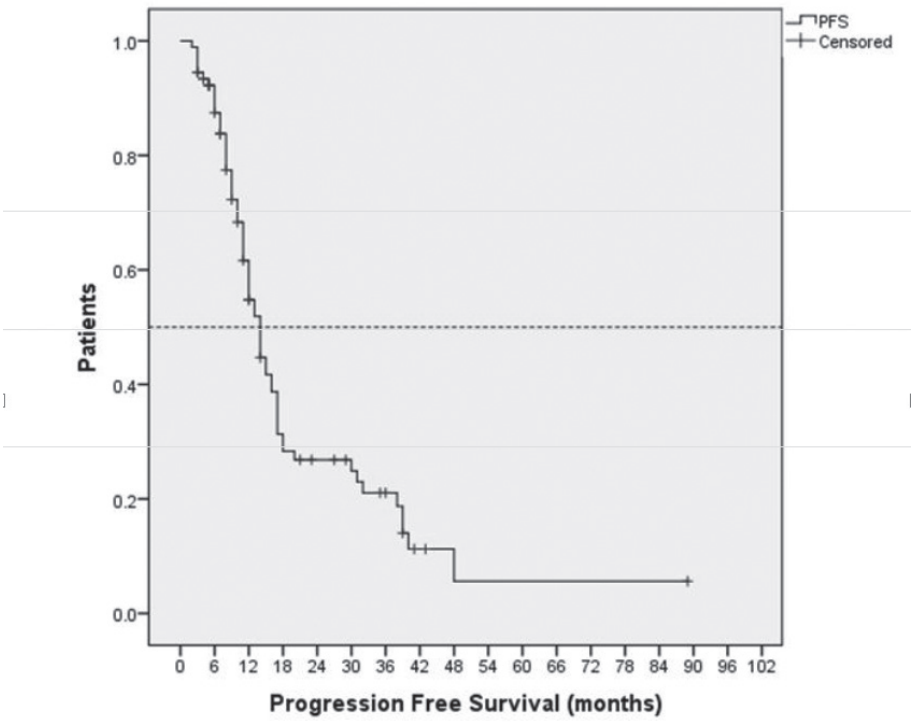
Treatment of the metastases	N (%)
Bone	*1*
Adrenal & pulmonary	*1*
Surgery	5 (5.5%)
Brain	*2*
Adrenal gland	*2*
Gamma knife	2 (2.2%)
Brain	*2*
RFA	1 (1.1%)
Liver	*1*

Overall survival and progression free survival

After a median follow-up of 35 months (range 3-89, 95%CI 23-47), 42% (N=38) of the patients died. Sixty-nine percent (N=63) of the patients developed recurrence disease of whom 59% died. One patient died without any recurrence detected after 15 months. Most recurrences where within the thorax (N=28, 44%), brain (N=22, 35%) and adrenal gland (N=8, 13%). Eleven (12%) recurrences occurred within the irradiated area, of which 6 (7%) were within the thorax and 5 recurrences occurred at the location of the metastasis (5%). Thirty-nine patients (43%) had a recurrence in same organ which was affected at diagnosis. At the time of analysis, 58% (N=53) patients were alive, with a median follow-up of 18 months (range 3-89, 95% CI 12-24). Twenty-seven (51%) of those had no recurrence after a median active follow-up of 10 months (range 3-89, 95% CI 5-15).

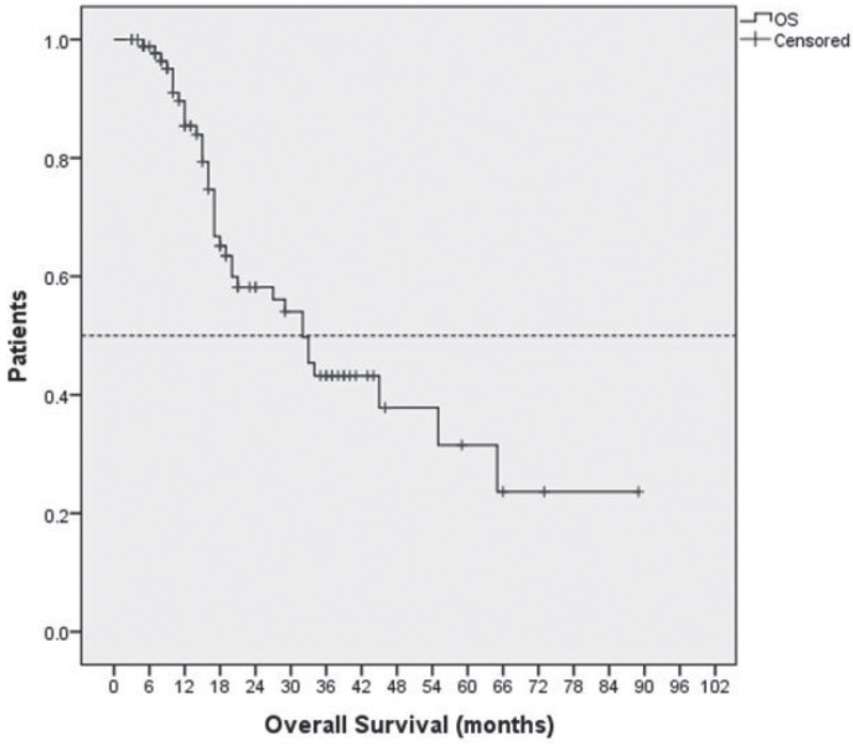
For the whole group, the median PFS was 14 months (range 2-89, 95% CI 12-16) and the median OS was 32 months (range 3-89, 95% CI 25-39). The 1- and 2-year OS were 85% and 58%, respectively. The 1- and 2-year PFS were 55% and 27%, respectively (**Figure 1 and 2**).

Univariate Cox proportional hazard analyses showed that squamous cell carcinoma (HR: 3.21, 95%CI: 1.26 – 8.14) and WHO-PS 1-2 (HR: 2.25, 95%CI: 1.15 – 4.40) were significantly associated with a lower OS. With respect to PFS, a higher T-stage (HR: 2.75, 95%CI: 1.25 – 6.08) was significantly associated with lower PFS (Table 4). In multivariate analyses, squamous cell carcinoma (HR: 3.63, 95%CI: 1.42 – 9.28) and WHO PS (HR: 2.51, 95%CI: 1.25 - 5.05) remained significant predictors for OS. For PFS, a higher T-stage (HR: 2.75, 95%CI: 1.25 – 6.08) remained as the only significant parameter in multivariate analyses (**Table 4**). There were no significant correlations between a higher T-stage and the development of distant metastasis or local recurrences.



Time (months)	0	6	12	18	24	30	36	42	54	60	66	72	78	84	90
N (patients no recurrence)	91	72	38	19	16	13	9	2	1	1	1	1	1	1	0

▲**Figure 1:**Progression free survival from time of diagnosis



Time (months)	0	6	12	18	24	30	36	42	54	60	66	72	78	84	90
N (patients alive)	91	82	59	39	28	25	17	10	6	4	2	2	1	1	0

▲**Figure 2:** Overall Survival from time of diagnosis

Table 4: Univariate and multivariate Cox regression analysis for Progression Free Survival (PFS) and Overall Survival (OS) . HR = Hazard Ratio, EGFR= epidermal growth factor receptor, NOS= not otherwise specified. WHO PS: World Healthcare Organization Performance Score. GTV = Gross Tumor Volume. * For GTV total volume the patients were ranked in 3 equal groups.

Variable	HR (OS) univariate	P-value (OS) univariate	HR (OS) multivariate	P-value (OS) multivariate	HR (PFS) univariate	P-value (PFS) univariate	HR (PFS) multivariate	P-value (PFS) multivariate
Sex								
Male	1.000				1.000			
Female	0.710	0.305			1.031	0.904		
Age								
< 57	1.000				1.000			
57-65	0.568	0.180			0.993	0.984		
65<	1.242	0.572			1.271	0.454		
WHO								
WHO PS 0	1.000		1.000		1.000			
WHO PS 1-2	0.667	***0.018***	2.512	***0.010***	0.812	0.105		
Pathology								
Adenoca	1.000		1.000		1.000			
Squamousca	3.207	***0.014***	3.630	***0.007***	2.042	0.087		
NOS	1.109	0.812	0.974	0.952	0.866	0.667		
Neuro-endodrinee	1.437	0.559	0.908	0.879	1.334	0.585		
EGFR (ref EGFR+)						0.744		
EGFR+	1.356	0.558			1.285	0.512		
EGFR -	2.148	0.135			1.093	0.822		
Thoracic stage								
Stage I&II	0.976	0.943			1.051	0.851		
Stage III	1.000				1.000			
T-stadium								
T0-1	1.000				1.000		1.000	
T2	1.947	0.146			2.070	***0.037***	2.070	***0.037***
T3	1.097	0.868			0.871	0.750	0.871	0.750
T4	2.509	0.084			2.753	***0.012***	2.753	***0.012***
N-stage								
N0	1.000				1.000			
N+	1.309	0.483			1.141	0.334		
GTV total volume*								
GTV-small	1.000				1.000			
GTV-intermediate	1.746	0.259			1.317	0.450		
GTV-large	2.416	0.069			1.381	0.379		
Total metastasis number								
1	1.000				1.000			
>1	0.684	0.603			0.975	0.954		

Variable	HR (OS) univariate	P-value (OS) univariate	HR (OS) multivariate	P-value (OS) multivariate	HR (PFS) univariate	P-value (PFS) univariate	HR (PFS) multivariate	P-value (PFS) multivariate
Location metastasis								
Brain	1.000				1.000			
Other than brain	0.858	0.648			0.944	0.827		
Systemic treatment 2								
yes	1.000				1.000			
no	0.973	0.955			0.963	0.916		
Systemic treatment								
Sequential	1.000				1.000			
Concurrent	0.847	0.785			1.791	0.131		
No systemic treatment	0.957	0.927			1.031	0.934		

Discussion

This observational study showed the results of 91 consecutive NSCLC patients diagnosed with oligometastatic disease who were selected for a radical treatment of the primary tumor and the metastasis. Stage IV NSCLC patients are considered incurable and are mainly treated with palliative intent. With the introduction of oligometastatic NSCLC disease as a separate entity, a more radical treatment approach is increasingly applied in current medical practice. However, the literature on outcome of patients with synchronous oligometastatic NSCLC treated radically is scarce. To our best knowledge this is one of the largest studies analyzing the outcome of a radical treatment with synchronous oligometastatic NSCLC patients.

The OS of 32 months and 1- and 2-year OS rates of 85% and 58% and a PFS of 14 months illustrate the favorable outcome in this patient group [3]. Compared to stage IV NSCLC patients who were treated with palliative chemotherapy (1-year OS of 29%) [3], OS is considerably better, which is at least in part due to the favorable prognostic profile of patients with oligometastatic disease [28].Uyterlinde et.al. [29] published the treatment outcome of locally advanced NSCLC patients treated with concurrent chemoradiation in our institute; the 2-year OS was 52% and PFS was 18.1 months. Although results may be confounded by selection bias, our current results show that the outcome of radical treatment of a selected population oligometastatic NSCLC patients is comparable with the treatment of locally advanced

NSCLC. De Ruysscher et al. [11] reported a prospective single arm phase III study for synchronous oligometastatic disease. The median OS and PFS in this study were 13.5 months and 12.1 months, respectively. The PFS is comparable to our results. The OS reported by De Ruysscher et al. is considerably lower. A possible explanation for this difference may be the time cohort 2008 to 2016 as compared to 2006-2010 in the study of De Ruysscher, as 2nd line systemic treatment in stage IV NSCLC patients has changed over recent years. Next to that, only 10% of our patient group received best supportive care (after progression), compared to 23% in the study by the Ruysscher et.al. The randomized study of Gomez et al. [14] reported a PFS of 12 months in the experimental arm (treatment with local consolidative therapy in patients without progression after first line chemotherapy) which is similar to our results. In our study population, at time of analysis, 5 patients (5%) were still alive 3 years after treatment without any signs of recurrence. De Ruysscher et al. observed that 15% of the patients did not show disease progression after 24 months. These data support the concept of oligometastatic disease in NSCLC and emphasize that these patients may be cured or have a favorable PFS.

In the literature different patient and tumor related prognostic factors are described for prolonged OS. We found that a good performance score and non-squamous cell carcinoma are favorable prognostic factors of OS. These results are in accordance with the results of Griffioen et al [15] and Flannery et al. [13]. Griffioen reported a better OS in patients who underwent surgery of the primary tumor, a smaller PTV of the primary tumor and non-squamous cell carcinoma. Flannery reported a better OS in patients with a Karnofsky performance score ≥ 90.

We acknowledge that the observational nature of this study has limitations. First, observational studies carry the risk of selection bias. There is a clear patient selection bias due to the procedure by selecting patients in a multidisciplinary tumor board meeting in a tertiary reference center which is obviously limiting the generalizability of our data. Only patients with favorable risk factors, like good performance score, no weight loss, few comorbidities and fit enough for chemotherapy, were selected for radical treatment. The majority of patients within our study population presented with adenocarcinoma (64%) and a single metastasis (85%). These are known favorable prognostic factors for oligometastatic NSCLC [7,9,15] and might have contributed to the favorable OS and PFS.

Although all of our patients had synchronous oligometastatic NSCLC at diagnosis, our study population remains heterogeneous since we included patients with different types of NSCLC histology, metastases in different organs and allowed different treatment regimens. Therefore, the statistical power of this analysis is too low to identify subgroups of patients who will benefit from a radical treatment.

In conclusion, radical local treatment of a selected group of NSCLC patients with good performance presenting with synchronous oligometastatic stage IV disease resulted in favorable long-term PFS and OS. Radical local treatment strategies should be part of future prospective studies and compared with standard therapy.

Reference

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA: a cancer journal for clinicians* 2015;65:87-108.
2. Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in australia, canada, denmark, norway, sweden and the uk: A population-based study, 2004-2007. *Thorax* 2013;68:551-564.
3. Group NM-AC. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: A systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2008;26:4617-4625.
4. Hellman S, Weichselbaum RR. Oligometastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1995;13:8-10.
5. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nature reviews Clinical oncology* 2011;8:378-382.
6. Baker S, Dahele M, Lagerwaard FJ, et al. A critical review of recent developments in radiotherapy for non-small cell lung cancer. *Radiation oncology* 2016;11:115.
7. Ashworth A, Rodrigues G, Boldt G, et al. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. *Lung cancer* 2013;82:197-203.
8. Kim C, Hoang CD, Kesarwala AH, et al. Role of local ablative therapy in patients with oligometastatic and oligoprogressive non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2017;12:179-193.
9. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clinical lung cancer* 2014;15:346-355.
10. De Rose F, Cozzi L, Navarria P, et al. Clinical outcome of stereotactic ablative body radiotherapy for lung metastatic lesions in non-small cell lung cancer oligometastatic patients. *Clinical oncology* 2016;28:13-20.
11. De Ruysscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: Long-term results of a prospective phase ii trial (nct01282450). *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012;7:1547-1555.
12. Downey RJ, Ng KK, Kris MG, et al. A phase ii trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis. *Lung cancer* 2002;38:193-197.
13. Flannery TW, Suntharalingam M, Regine WF, et al. Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. *International journal of radiation oncology, biology, physics* 2008;72:19-23.
14. Gomez DR, Blumenschein GR, Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. *The Lancet Oncology* 2016.

15. Griffioen GH, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (nsclc): Patient outcomes and prognostic factors. *Lung cancer* 2013;82:95-102.
16. Hasselle MD, Haraf DJ, Rusthoven KE, et al. Hypofractionated image-guided radiation therapy for patients with limited volume metastatic non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* 2012;7:376-381.
17. Hendriks LE, Derks JL, Postmus PE, et al. Single organ metastatic disease and local disease status, prognostic factors for overall survival in stage iv non-small cell lung cancer: Results from a population-based study. *European journal of cancer* 2015;51:2534-2544.
18. Khan AJ, Mehta PS, Zusag TW, et al. Long term disease-free survival resulting from combined modality management of patients presenting with oligometastatic, non-small cell lung carcinoma (nsclc). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* 2006;81:163-167.
19. Lopez Guerra JL, Gomez D, Zhuang Y, et al. Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. *International journal of radiation oncology, biology, physics* 2012;84:e61-67.
20. Palma DA, Haasbeek CJ, Rodrigues GB, et al. Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic tumors (sabr-comet): Study protocol for a randomized phase ii trial. *BMC cancer* 2012;12:305.
21. Parlak C, Mertsoylu H, Guler OC, et al. Definitive chemoradiation therapy following surgical resection or radiosurgery plus whole-brain radiation therapy in non-small cell lung cancer patients with synchronous solitary brain metastasis: A curative approach. *International journal of radiation oncology, biology, physics* 2014;88:885-891.
22. Pfannschmidt J, Dienemann H. Surgical treatment of oligometastatic non-small cell lung cancer. *Lung cancer* 2010;69:251-258.
23. Plones T, Osei-Agyemang T, Krohn A, et al. Surgical treatment of extrapulmonary oligometastatic non-small cell lung cancer. *The Indian journal of surgery* 2015;77:216-220.
24. Rusthoven CG, Yeh N, Gaspar LE. Radiation therapy for oligometastatic non-small cell lung cancer: Theory and practice. *Cancer journal* 2015;21:404-412.
25. Salama JK, Schild SE. Radiation therapy for oligometastatic non-small cell lung cancer. *Cancer metastasis reviews* 2015;34:183-193.
26. Sheu T, Heymach JV, Swisher SG, et al. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. *International journal of radiation oncology, biology, physics* 2014;90:850-857.
27. Xanthopoulos EP, Handorf E, Simone CB, 2nd, et al. Definitive dose thoracic radiation therapy in oligometastatic non-small cell lung cancer: A hypothesis-generating study. *Practical radiation oncology* 2015;5:e355-363.
28. Treasure T. Oligometastatic cancer: An entity, a useful concept, or a therapeutic opportunity? *Journal of the Royal Society of Medicine* 2012;105:242-246.
29. Uyterlinde W, Belderbos J, Baas C, et al. Prediction of acute toxicity grade >/= 3 in patients with locally advanced non-small-cell lung cancer receiving intensity modulated radiotherapy and concurrent low-dose cisplatin. *Clinical lung cancer* 2013;14:541-548.

CHAPTER 4

INTRA THORACIC ANATOMICAL CHANGES IN LUNG CANCER PATIENTS DURING THE COURSE OF RADIOTHERAPY

Margriet Kwint*, Sanne Conijn*, Eva Schaake, Joost Knegjens, Maddalena Rossi, Peter Remeijer, Jan-Jakob Sonke, Jose Belderbos

*** Both authors have contributed equally**

Radiother Oncol. 2014;113(3):392-397. doi:10.1016/j.radonc.2014.10.009

Background and purpose

Conebeam-CT (CBCT) guidance is often used for setup verification of lung cancer patients treated with radiotherapy. The purpose of this study was to quantify intra-thoracic anatomical changes (ITACs) during the radiotherapy treatment and to hand over a decision support system to guide the radiation therapy technologist and radiation oncologist in prioritizing these changes.

Materials and Methods

1793 CBCT-scans of 177 lung cancer patients treated in 2010 in our institute with radical radiotherapy were evaluated. Our decision support system: "the traffic-light protocol", was retrospectively applied to these CBCT-scans. The protocol has four levels: red (immediate action before treatment), orange (action before next fraction), yellow (no action required) and green (no change).

Results

In 128 patients (72%), 210 ITACs were observed with a maximum level of red, orange and yellow in 12%, 36% and 24% respectively. Types of observed ITACs were, tumor regression (35%), tumor baseline shift (27%), changes in atelectasis (19%), tumor progression (10%), pleural effusion (6%) and infiltrative changes (3%).

Conclusions

ITACs have been observed in 72% of all lung cancer patients during the course of radical radiotherapy. The clinical relevance of the proposed ITAC classification in lung radiotherapy needs to be validated in a prospective analysis.

Introduction

In the Netherlands, about 12000 new lung cancer patients are diagnosed annually. 80% of these patients are medically or technically inoperable at diagnosis [1]. Patients with inoperable locally advanced lung cancer are often treated with radical radiotherapy and depending on physical condition and/or tumor stage with or without chemotherapy. The overall treatment time of the radiotherapy courses in our clinic is 5/6 weeks and it is generally assumed that the anatomy of the patient is stable during this treatment. However, during this course of radiotherapy several anatomical changes may occur, such as atelectasis, infiltrative changes, tumor progression or regression and pleural effusion [2-14].

With the introduction of advanced image-guided systems like kilovoltage (kV) cone-beam computed tomography (CBCT), megavoltage (MV) CBCT, and tomotherapy, we have the ability to visualize the tumor and organs at risk (OAR) in 3D [15,16]. These modalities primarily minimize target misalignment and setup-error [9]. Many studies investigate setup precision in lung radiotherapy [17,18]. However, only a few studies reported anatomical changes during the course of lung radiotherapy [9,11,19]. In clinical practice repetitive CBCT's make us aware of intra thoracic anatomical changes (ITACs) during the course of a radical treatment. In the Netherlands, CBCT's are typically analyzed by radiation therapy technologists (RTTs), the radiation oncologist is only informed when a change is observed. In our institute, we developed an action level protocol as a decision support system to guide the RTT in prioritizing these changes. In this study, we quantified ITACs during radiotherapy and present a decision support system (Traffic Light Protocol).

Methods and materials

Patient selection

The Traffic Light Protocol was introduced clinically in our institute in 2011. All CBCT's of lung cancer patients radically treated with radiotherapy or chemo-radiotherapy (≥44Gy) in our institute in 2010, were retrospectively analyzed based on this Traffic Light Protocol.

Patients treated with stereotactic radiotherapy were excluded as they had a different decision protocol. Inclusion criteria for this study were radical treatment with

radiotherapy (>44 Gy), histology or cytology proven lung cancer and image guided radiotherapy (IGRT) with the use of 3 or 4D-CBCT. All CBCT-scans were available for all patients. Several radiotherapy regimens, all planned with Intensity Modulated Radiotherapy (IMRT) and concurrent or sequential chemotherapy or radiotherapy alone were included.

Radiotherapy preparation

A 3D-midventilation-CT (MidV-CT) was selected for all patients from a respiration correlated 4DCT, in which the moving tumor was closest to its time-averaged mean position [20]. The gross tumor volume (GTV) and pathological lymph nodes were delineated on the MidV-CT. A recent flu-deoxyglucose-positron-emission-tomography-(FDG-PET)-scan was registered to the MidV-CT[21]. The GTV was expanded to a planning target volume (PTV) using margins of 12 mm +¼ of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. A uniform PTV margin of 12 mm was used for the lymph nodes [22] according to our institutional protocol. The planning-constraints used for the OAR were; esophagus V35<65% (physical dose), Mean Lung-Dose ≤20Gy (EQD_2 α/β=3Gy), spinal cord ≤50Gy (EQD_2 α/β=2Gy), total heart ≤40Gy, ⅔ of the heart ≤50Gy and ⅓ of the heart ≤66Gy (physical dose). Equally spaced, 7-field IMRT-plans were designed using 6/10 MV photons and direct machine parameter optimization (Pinnacle version 9.0, Philips, Best, the Netherlands) on the homo-lateral lung [23]. The prescription-dose was specified at a representative point in the PTV. The dose distribution within 99% of the PTV was >90% and <115% of the prescribed dose.

Setup correction protocol

An off-line shrinking action level setup correction protocol was used for all patients [24] with Nmax=3 and α=9mm. For this off-line shrinking action level setup correction protocol, CBCT's were acquired the first three fractions using Elekta Synergy 4.2 (Elekta Oncology Systems Ltd., Crawley, UK). If no correction was necessary (average setup error over 3 fractions <5.2mm in each direction) then weekly follow-up scans were acquired. If a correction was required, the protocol restarted with three fractions with CBCT verification. This resulted in a minimum of 7 CBCT's per patient. 4D-CBCT were acquired if the motion of the tumor, measured on the 4DCT, was ≥8 mm. The CBCT's were registered, by two RTTs, to the MidV-CT based on the bony anatomy of the vertebrae [25].

Decision support system

A team of dedicated CBCT RTTs, radiation oncologists and physicists evaluated examples of collected ITACs. Four types of urgency levels were defined (**figure 1**): A protocol for communication and/or consultation was defined for each urgency level.

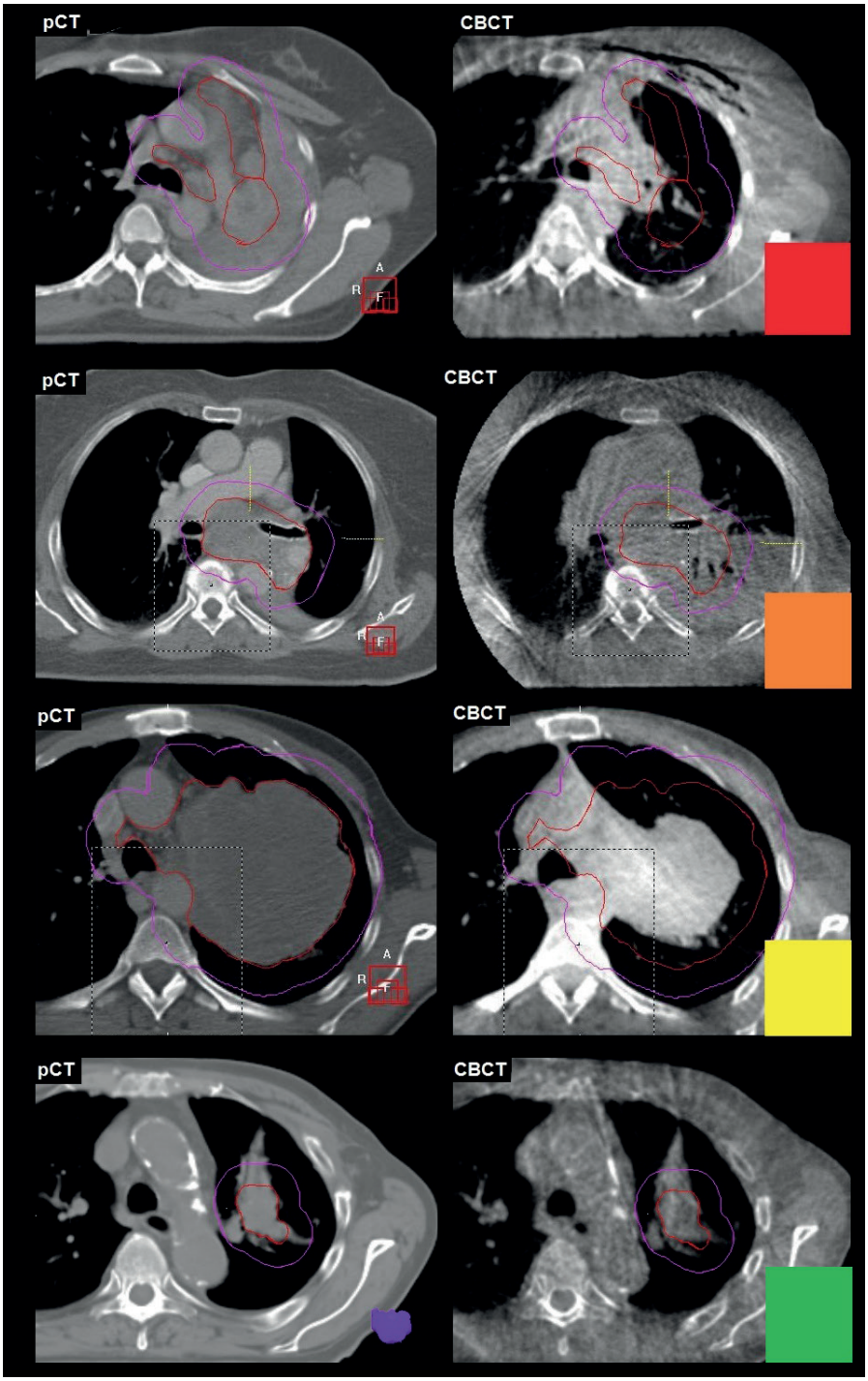
1. Action level red: The GTV is outside the PTV due to ITACs. The radiation oncologist is called immediately and treatment is only given when approved by the radiation oncologist.

2. Action level orange: The GTV is just inside the PTV due to ITACs. The radiation oncologist is notified by email and has to respond before the next fraction. Further diagnostics are considered as a result of the ITAC.

3. Action level yellow: There is an ITAC visible but the GTV is well inside the PTV. The radiation oncologist is notified by email about the ITAC but no response is necessary and treatment may continue.

4. Action level green: No change visible. No action needed.

The Traffic Light Protocol is practical guideline to the RTTs visual inspection of the patients CBCT in the absence of the possibility to quantify the dosimetric influence of ITACs immediately after a CBCT is made. Note that a CBCT is not of diagnostic quality. A visual assessment that the CBCT visualized GTV is (well) within the PTV gives confidence but no guarantees that the tumor receives adequate dose. The traffic light color therefore reflects a risk assessment of the occurrence of clinically relevant dosimetric changes. In case of an ITAC, the RTT informs the radiation oncologist. The radiation oncologist and clinical physicist make an estimation of the dosimetric influence of the ITAC on the tumor and/or OAR. When is estimated that the dosimetric influence is relevant for treatment outcome, a new planning-CT and possibly adaptive treatment plan will be made.


pCT
CBCT
pCT
CBCT
pCT
CBCT
pCT
CBCT

◂**Figure 1:** Four examples of the traffic light protocol. left: planning CT (pCT), right: cone beam CT (CBCT). Purple: planning target volume (PTV); Red: gross tumor volume (GTV). First row: example of level red change; this patient had cT4N2M0 NSCLC and was treated with 24x 2.75 Gy. This is the CBCT of week 3, the atelectasis resolved and this resulted in a tumor shift outside PTV. Second row: example of level orange change; this patient had cT4N2M0 NSCLC and was treated with 24x 2.75 Gy. In week 1 the CBCT showed development of atelectasis without a tumor shift. Third row: example level yellow change; this patient had cT4N2M0 NSCLC and was treated with 17x 3Gy. This CBCT shows regression in week 3 of the treatment. Fourth row: example level green, no change. Recurrence, the patient was treated with 17x 3Gy. The image is the CBCT of fraction 15.

Intra Thoracic Anatomical Changes

All CBCT's were added to a database. All CBCT's were scored retrospectively and compared to the planning-CT (bony anatomy, carina, trachea and mediastinal contour were used to compare the CBCT with the planning-CT). Two IGRT-specialists independent of each other visually evaluated every CBCT. For each CBCT, the observed ITACs were scored: changes in atelectasis, infiltrative changes, pleural effusion, considerable tumor baseline shift, tumor regression and tumor progression. If an ITAC was detected, the date of the first occurrence of the highest level (red, orange, yellow or green) of each ITAC was compiled. Furthermore, subsequent actions, e.g. a repeat radiotherapy planning-CT-scan or re-planning were scored.

Statistical analysis

To evaluate the ITACs during the course of radiotherapy SPSS for windows software, version 20, was used for statistical analysis. Firstly, descriptive statistics were used to analyze the number of ITACs. Thereafter Spearman's rank correlation coefficients were used to analyze if there were any significant correlations between progression and an adaptive treatment plan with the following parameters: tumor regression, tumor baseline shift, changes in atelectasis, pleural effusion, infiltrative changes, traffic light level of changes, changes in the first week, patient characteristics, tumor stage, tumor location, type of treatment and time interval between planning-CT and first day of treatment.

Results

Patients

Between January 2010 and December 2010, 226 patients were treated with a radical radiotherapy scheme for lung cancer. A group of 177 patients with complete data were selected (**Table 1**). Mean age was 66 years (range 32-87). A total of 1793 CBCT-scans from these 177 patients were evaluated. Ninety-seven (55%) patients were treated with concurrent chemoradiation (CCRT), 57 (32%) with radiotherapy only (RT), 23 (13%) received sequential chemoradiation (SeqCRT) and 17 patients were irradiated after surgery.

Table 1: Patient characteristics

Characteristic	***No patients (N=177)***	***%***
Gender		
Male	112	63
Female	65	37
WHO		
0	13	7
1	124	70
2	39	22
3	1	1
Stage		
1A	4	2
1B	1	1
IIA	11	6
IIB	10	6
IIIA	71	40
IIIB	63	36
IV	6	3
recurrence	11	6
Tumor location		
Right upper lob	58	33
Right middle lob	13	7
Right lower lob	18	10
Left upper lob	49	28
Left lower lob	20	11
mediastinal	19	11
Histology		
Adenocarcinoma	42	24
Squamuscellcarcinoma	44	25
Large cell/not specified	70	39
Small cell lung cancer	21	12

Characteristic	*No patients (N=177)*	*%*
RT-schedule		
24x2.75 Gy	113	64
17x3 Gy	31	18
25x2 Gy	25	14
30x2 Gy	3	1.5
30x2.25 Gy	2	1
30x1,5 Gy (2 times a day)	1	0.5
25x1.8 Gy	1	0.5
33x2 Gy	1	0.5

Intra thoracic anatomical changes

ITACs were observed in 128 patients (72%). In total 200 ITACs were scored (**Table 2**). Sixty patients (47%) had 1 ITAC, 46 patients (36%) 2 ITACs and in 22 patients (17%) >2 ITACs were observed. The highest ITAC scored per patient was level red, orange and yellow in 12%, 36% and 24% respectively. 28% off the patients had no observed ITACs (level green). Sixteen patients (9%) required an adapted treatment plan to account for the changed anatomy, for which 14 received a new plannings-CT-scan (8%). It took 1 to 3 working days to generate and implement the adapted plan (mean 2.2 working days). Most ITACs occurred in the first week (55%). In week 2, 3, 4 and 5, in 16%, 15%, 8% and 6% ITACs were observed respectively. Types of ITACs scored were evident regression (35%), tumor baseline shift (27%), changes in atelectasis (19%), tumor progression (10%), pleural effusion (6%) and infiltrative changes (3%) (total N=210 ITACs in 177 patients).

The incidence of ITACs was higher in the CCRT- (77%) and SeqCRT-group (74%) compared to the RT-group (52 %) (p=.265). Similarly, the incidence of level red changes was higher in the CCRT- (16%) and SeqCRT-group (12%) compared to the RT-group (0%) (p=.204).

In 28(16%) patients atelectasis developed (N=16) or increased (N=12). This occurred mainly in the first week (N=25, 89%). In the other 3 patients atelectasis developed in week 2 (N=2) or week 3 (N=1). These ITACs had mostly level red (N=10, 36%) and level orange (N=15, 53%), the other 3 (11%) were level green.

Decrease or resolving of atelectasis occurred in 12 patients (7%). This ITAC was not typically scored in a specific week; N=3 in week 1 and 2 (25%), N=5 in week 3 (42%) and N=1 in week 5 (8%). Level red was observed in 5 patients (42%), level orange in 4 patients (33%) and level yellow in 3 patients (25%).

Infiltrative changes were rarely seen as ITACs during the radiotherapy course. This appeared in 5 patients (3%) and disappeared in 2 patients (1%) during treatment. This was observed in 4 patients in week 1 (57%), 2 patients in week 2 (29%) and in 1 patient in week 3 (14%). The urgency levels of these changes were; level red in 1 patient (14%), level orange (43%) in 3 patients and level yellow in 3 patients (43%). These level red and orange changes were all associated with regression.

Pleural effusion was observed in 24 patients (14%). In 20 patients, pleural effusion appeared or increased and in 4 patients pleural effusion disappeared or decreased. These changes were mainly seen in week 1 (N=9,38%), thereafter in 6 (25%), 4 (17%), 3 (13%), and 2 (8%) patients in week 2,3,4 and 5 respectively. The levels corresponding with these changes were level red in 5 patients (21%), level orange in 14 patients (58%) and level yellow in 5 patients (21%).

A tumor baseline shift is a visual difference in the tumor position between the planning-CT and CBCT after a bony anatomy match[26]. In 56 patients (32%), a tumor baseline shift was observed. These baseline shifts remained within the PTV (level orange, N=46, 82%) while in 10 patients (18%) the tumor had moved outside the PTV (level red). The onset of these tumor baseline shifts were mainly observed in the first week (48%). Some of these tumor baseline shifts were combined with regression (N=24), atelectasis (N=19) and/or progression (N=8) of the tumor, which in turn, themselves may cause a tumor baseline shift.

Tumor progression was observed in 22 patients (12%). This occurred in week 1 for 21 patients (95%) and in 1 patient (5%) in week 2. This was level red in 9 patients (41%), level orange in 9 patients (41%) and level green in 4 patients (18%). In the 22 patients with tumor progression, subsequent tumor regression was seen in 16 patients at a later stage during the radiotherapy course.

Tumor regression was observed in 73 patients (41%). The onset of the observed regression started in week 1 in 3 patients (2%) and in week 2 for a further 10 patients (14%). All of these patients were treated with CCRT, except for one patient who only received RT. Most regression cases was first observed in week 3 (N=27, 37%) and week 4 (N=23, 32%), while in 10 patients (14%) regression started in week 5. The levels corresponding to regression were mainly level yellow (N=35, 48%), thereafter level orange (N=26, 15%) and level red (N=12, 16%). Remarkably, in the 12 patients with a level red change, 8 patients had a change in atelectasis (4x increase and 4x

decrease) and in 5 of these 8 patients, a baseline tumor shift was also seen. In total 7 tumor baseline shifts were scored in patients with a level red regression. Therefore, regression was not always the sole cause of level red. Level red was scored due to changes in atelectasis and tumor baseline shifts in 10 patients, which was a result of regression.

The median time interval between planning-CT and start of the treatment (first CBCT) was 10 days (range 2-20 days). No significant correlation was found between this time interval and tumor progression (p=.270), level red change (p=.783) and new radiotherapy treatment plans (p=.744). Patients with stage III lung cancer (N=134) had a significantly higher chance of receiving a repeat treatment plan if the time interval between the planning-CT and start of treatment was more than one week (p=.040; correlation coefficient=.178). Tumor progression had a higher chance of a level red change (p=.001; correlation coefficient=.286) and development of this change in the first week (p=<.001; correlation coefficient=.431). There was also a higher chance of developing atelectasis (p=.028; correlation coefficient=.165) and tumor regression (p=.001; correlation coefficient=.241) observed in patients with tumor progression. The decision for a new treatment plan correlated significantly with tumor progression (p=.001), atelectasis (p=.006), tumor baseline shift (p=.005), an ITAC in the first week (p=.012) and level red change (p=<.001). There was no significant correlation found with patient characteristics (mentioned in Table 1), and ITACs.

Table 2: Intra thoracic anatomical changes (N=210) in 128 patients

ITACs	N
Atelectasis developing/increasing	28 (13%)
Atelectasis resolving/decreasing	12 (6%)
Tumor baseline shift	56 (27%)
Infiltrative changes	6 (3%)
Tumor regression	73 (35%)
Tumor progression	22 (10%)
Pleural effusion	13 (6%)
Total	210 (100%)

Discussion

To the best of our knowledge, this is the first study where ITACs observed on the CBCT have been systematically analyzed and a decision protocol implemented on how to deal with these changes. This study showed that ITACs frequently occurred during radical radiotherapy of lung cancer patients. During radiotherapy, it is important to have knowledge of and act accordingly to these changes. Many studies have described set-up errors, changes in tumor volume or regression during treatment [2-13,17,18]. We observed ITACs in 72% (N=128) of all lung cancer patients during the radical radiotherapy course. Regression during treatment was described by several groups [2-14,18]. Knap et.al.[5] reported that ⅓ of lung cancer patients undergoing (chemo-) radiotherapy achieved significant tumor shrinkage at the end of radiotherapy. This is in accordance with our findings that in 36% of the patients regression was visible on the CBCT during treatment. Siker et.al. [8] studied tumor volume change on MV-CT and found similar results; in 32% of the patients, regression was visible. Bosmans et.al. [2] studied tumor volume changes in 23 patients in the first two weeks of a course of accelerated RT and reported a variation in tumor volume change: a 30% increase and 30% decrease. Decreased volume was observed from week 2 onwards. This is in accordance with our findings, where only in 2% of patients demonstrated regression in week 1. In our experience, informing the patient about tumor regression seen during treatment, helps them to cope with their side-effects during radiotherapy. Bosman et.al. found in 17% (4/23) of the patients an increase in tumor volume, mainly seen in week 1. This corresponds with our findings that in 12% of patients, tumor progression was visible on CBCT, mainly scored in week 1. It is possible that tumor progression may occur between the planning-CT and start of irradiation. The initial volume increase may be due to tumor progression, edema or inflammation. This study did not show a significant relationship in the time interval between planning-CT and start of treatment and tumor volume increase in the whole group. However, in stage III patients there was a significantly higher chance of adapting a treatment plan due to ITACs, if the time interval between the planning-CT and start of the treatment is more than one week. Therefore, it is necessary to keep this time interval as short as possible. Tumor progression correlated highly with the development of atelectasis and tumor regression. This could be explained if atelectasis developed due to progression. Progressive tumors may have a higher proliferation rate and therefore be more radiosensitive, which could explain the correlation with regression[27]. In our study, the CBCT's were scored visually. This

may have caused a bias in the observation of progression and regression because this could be more pronounced in larger tumors.

Besides tumor progression and regression, there was a high incidence of other ITACs during treatment. Møller et. al. [19] found in 23% of 163 lung cancer patients changes in lung density on CBCT due to atelectasis, pleural effusion or infiltrative changes. Tumor volume changes were excluded in this study. This is in accordance to our findings, with an incidence of 28% ITACs due to atelectasis, pleural effusion and infiltrative changes.

Due to the high incidence and large variability of ITACs it is therefore important that repeated (CB) CT's are made during the course of radiotherapy and that RTTs are well trained to evaluate these scans. In current clinical practice, more and more radiotherapy departments are implementing CBCT's. A clear decision protocol could be helpful in guiding the radiation oncologists and RTTs in evaluating changes visible on CBCT. The decision protocol that was implemented in our institute, contains illustrative examples of each of the four urgency levels (figure 1)[28]. All RTTs are trained in using these urgency levels. There are no practical limitations to implement this protocol in other radiotherapy centers.

This study is based on weekly CBCT-imaging. In this study, we were unable to distinguish whether the ITAC occurred on the first day following the weekly CBCT or almost a week later before the next weekly CBCT. From January 2012 on, we have implemented daily CBCT guidance for lung cancer patients in our institute in order to assess ITACs as soon as possible and for accurate patient alignment.

This is the first investigation on ITAC during RT on CBCT. This study was done retrospectively with weekly CBCT's. The results of this study needs to be validated in a prospective study to find out if CBCT's needs to be part of routine clinical practice in radical irradiated lung cancer patients. The dosimetric impact of ITACs on the dose distribution is subject of further research.

In conclusion, ITACs have been observed in 72% of all lung cancer patients during the course of radical radiotherapy. In 12% of the patients, the radiation oncologist was required to respond immediately and in 8% of the patients, a new planning-CT-scan was made to mitigate the risk of tumor under dosage. The clinical relevance of the proposed ITAC classification in the lung radiotherapy needs to be validated in a prospective analysis.

Reference:

1. van der Drift MA, Karim-Kos HE, Siesling S, et al. Progress in standard of care therapy and modest survival benefits in the treatment of non-small cell lung cancer patients in the netherlands in the last 20 years. *J Thorac Oncol* 2012;7:291-298.
2. Bosmans G, van Baardwijk A, Dekker A, et al. Intra-patient variability of tumor volume and tumor motion during conventionally fractionated radiotherapy for locally advanced non-small-cell lung cancer: A prospective clinical study. *Int J Radiat Oncol Biol Phys* 2006;66:748-753.
3. Britton KR, Starkschall G, Tucker SL, et al. Assessment of gross tumor volume regression and motion changes during radiotherapy for non-small-cell lung cancer as measured by four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys* 2007;68:1036-1046.
4. Fox J, Ford E, Redmond K, et al. Quantification of tumor volume changes during radiotherapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;74:341-348.
5. Knap MM, Hoffmann L, Nordsmark M, et al. Daily cone-beam computed tomography used to determine tumour shrinkage and localisation in lung cancer patients. *Acta Oncol* 2010;49:1077-1084.
6. Kupelian PA, Ramsey C, Meeks SL, et al. Serial megavoltage ct imaging during external beam radiotherapy for non-small-cell lung cancer: Observations on tumor regression during treatment. *Int J Radiat Oncol Biol Phys* 2005;63:1024-1028.
7. Rit S, Kuijf H, van Kranen S, et al. Computer assisted analysis of lung tumor regression during radiotherapy. *International Conference on the Use of Computers in Radiation Therapy* 2010.
8. Siker ML, Tome WA, Mehta MP. Tumor volume changes on serial imaging with megavoltage ct for non-small-cell lung cancer during intensity-modulated radiotherapy: How reliable, consistent, and meaningful is the effect? *Int J Radiat Oncol Biol Phys* 2006;66:135-141.
9. Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. *Semin Radiat Oncol* 2010;20:94-106.
10. Tanyi JA, Fuss MH. Volumetric image-guidance: Does routine usage prompt adaptive re-planning? An institutional review. *Acta Oncol* 2008;47:1444-1453.
11. van Zwienen M, van Beek S, Belderbos J, et al. Anatomical changes during radiotherapy of lung cancer patients. *Int J Radiat Oncol Biol Phys* 2008;72:supplement.
12. Werner-Wasik M, Xiao Y, Pequignot E, et al. Assessment of lung cancer response after nonoperative therapy: Tumor diameter, bidimensional product, and volume. A serial ct scan-based study. *Int J Radiat Oncol Biol Phys* 2001;51:56-61.
13. Woodford C, Yartsev S, Dar AR, et al. Adaptive radiotherapy planning on decreasing gross tumor volumes as seen on megavoltage computed tomography images. *Int J Radiat Oncol Biol Phys* 2007;69:1316-1322.
14. Erridge SC, Seppenwoolde Y, Muller SH, et al. Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. *Radiother Oncol* 2003;66:75-85.
15. Korreman S, Rasch C, McNair H, et al. The european society of therapeutic radiology and oncology-european institute of radiotherapy (estro-eir) report on 3d ct-based in-room image guidance systems: A practical and technical review and guide. *Radiother Oncol* 2010;94:129-144.

16. Verellen D, De Ridder M, Storme G. A (short) history of image-guided radiotherapy. *Radiother Oncol* 2008;86:4-13.
17. Borst GR, Sonke JJ, Betgen A, et al. Kilo-voltage cone-beam computed tomography setup measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device. *Int J Radiat Oncol Biol Phys* 2007;68:555-561.
18. de Boer HC, van Sornsen de Koste JR, Senan S, et al. Analysis and reduction of 3d systematic and random setup errors during the simulation and treatment of lung cancer patients with ct-based external beam radiotherapy dose planning. *Int J Radiat Oncol Biol Phys* 2001;49:857-868.
19. Moller DS, Khalil AA, Knap MM, et al. Adaptive radiotherapy of lung cancer patients with pleural effusion or atelectasis. *Radiother Oncol* 2014;110:517-522.
20. Wolthaus JW, Schneider C, Sonke JJ, et al. Mid-ventilation ct scan construction from four-dimensional respiration-correlated ct scans for radiotherapy planning of lung cancer patients. *Int J Radiat Oncol Biol Phys* 2006;65:1560-1571.
21. Lavrenkov K, Partridge M, Cook G, et al. Positron emission tomography for target volume definition in the treatment of non-small cell lung cancer. *Radiother Oncol* 2005;77:1-4.
22. van Herk M. Errors and margins in radiotherapy. *Semin Radiat Oncol* 2004;14:52-64.
23. Schwarz M, Alber M, Lebesque JV, et al. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2005;62:561-570.
24. Bel A, Vos PH, Rodrigus PT, et al. High-precision prostate cancer irradiation by clinical application of an offline patient setup verification procedure, using portal imaging. *Int J Radiat Oncol Biol Phys* 1996;35:321-332.
25. Schaake EE, Belderbos JS, Buikhuisen WA, et al. Mediastinal lymph node position variability in non-small cell lung cancer patients treated with radical irradiation. *Radiother Oncol* 2012;105:150-154.
26. Sonke JJ, Lebesque J, van Herk M. Variability of four-dimensional computed tomography patient models. *Int J Radiat Oncol Biol Phys* 2008;70:590-598.
27. Joiner M, van der Kogel A. Basic clinical radiobiology, 4 ed.: Hodder Arnold; 2009.
28. http://www.avl.nl/media/291805/xvi_engelse_protocols_16_7_2014.pdf

CHAPTER 5

THE PREDICTIVE VALUE OF VOLUMETRIC CHANGES MEASURED ON CONE BEAM-CT (CBCT) DURING RADIOTHERAPY FOR CCRT IN NSCLC PATIENTS

Margriet Kwint, Barbara Stam, Cecile Proust-Lima, Viviane Philipps, Trynke Hoekstra , Else Aalbersberg, Maddalena Rossi, Jan-Jakob Sonke, Jose Belderbos, Iris Walraven

Radiother Oncol. 2020;146:44-51. doi:10.1016/j.radonc.2020.02.002

Introduction

The aim of this study was to identify subgroups of locally advanced NSCLC patients with a distinct treatment response during concurrent chemoradiotherapy (CCRT). Subsequently, we investigated the association of subgroup membership with treatment outcomes.

Methods

Three hundred and ninety four NSCLC-patients treated with CCRT between 2007-2013 were included. Gross Tumor Volume (GTV) during treatment was determined and relative GTV-volume change from the planning-CT was subsequently calculated. Latent Class Mixed Modeling (LCMM) was used to identify subgroups with distinct volume changes during CCRT. The association of subgroup membership with overall survival (OS), progression free survival (PFS) and local regional control (LRC) was assessed using cox regression analyses.

Results

Three subgroups of GTV-volume change during treatment were identified, with each subsequent subgroup showing a more profound reduction of GTV during treatment. Surprisingly, no associations between subgroup membership and OS, PFS nor LRC were observed. Nonetheless, baseline GTV (HR 1.42; 95%CI 1.06–1.91) was significantly associated with OS.

Conclusions

Three different subgroups of GTV-volume change during treatment were identified. Surprisingly, these subgroups did not differ in their risk of treatment outcomes. Only patients with a larger GTV at baseline had a significantly worse OS. Therefore, risk stratification at baseline might already be accurate in identifying the best treatment strategy for most patients.

Introduction:

Patients with locally advanced non–small cell lung cancer (LA-NSCLC) are preferably treated with concurrent chemoradiation (CCRT). Although this treatment has a curative intent, overall survival (OS) is poor with 44-59% surviving at 2 years (1-3). In order to distinguish patients with better or worse OS, it is important to build accurate prediction models for individual treatment outcomes. Current prediction models mainly use baseline characteristics to predict treatment outcomes (4-11). An important step to improve these prediction models might be to incorporate longitudinal data of tumor volume change derived during treatment.

The predictive value of tumor volume changes during treatment has been studied previously (12-15). Although these studies hinted towards a predictive potential, the observed associations were inconsistent and the performed studies were of limited quality due to small sample sizes. Furthermore, the performed analyses could have been too simplistic. For example, observed GTV-changes during treatment were dichotomized below or above the median (13-15). The assumption that 2 groups (above/below median) represent the treatment response of all NSCLC patients might be a misconception (16). In order to identify various subgroups of patients with distinct treatment responses, more advanced statistical techniques, such as latent class mixed modelling, could be useful (17-20). The use of image guided radiotherapy (IGRT) (e.g. Cone Beam-CT(CBCT)), resulted in an increase of readily available imaging data of tumor volume during radiation treatment(21). Consequently, this data could be used as a longitudinal parameter for treatment outcomes. Subgroups with particular tumor volume changes could have worse/better outcomes compared to others. The addition of this more dynamic information might improve the prognostic accuracy of the current baseline prediction models (4-10). Therefore, the aim of this study is to identify subgroups of LA-NSCLC patients showing distinct treatment responses during CCRT and to investigate whether the identified subgroups are associated with treatment outcomes.

Materials and Methods

Patient selection

An observational study was performed, including 394 consecutive patients treated with CCRT for cytologically or histologically proven LA-NSCLC in our institute between 2007 and 2013. Medical records and treatment characteristics of these patients were registered. The concurrent chemotherapy regimen consisted of daily low-dose cisplatin intravenous (6 mg/m²) 1-2h before irradiation. All patients were treated with intensity modulated radiotherapy (IMRT) to 66Gy/24 fractions to the primary tumor and the involved mediastinal lymph nodes in, 5 times per week on a linear accelerator equipped with a CBCT. Exclusion criteria were: other CCRT schedules or the absence of available CBCT-data. The Institutional Review Board of our institute approved the study for retrospective data collection according to the European Privacy Law

Radiotherapy preparation

A 3D-midposition-CT (MidP-CT) was selected for all patients from a respiration correlated 4D-planning-CT, in which the moving tumor was reconstructed at time average mean position (22). A recent FDG-PET-scan was registered to the MidP-CT, and the gross tumor volume (GTV) and all pathological lymph nodes were delineated on the MidP-CT. The GTV was expanded to a planning target volume (PTV) using margins of 12 mm+¼ of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. A uniform PTV margin of 12 mm was used for the lymph nodes (23) according to our institutional protocol. Organs at risk were delineated according to the institutional protocol: heart, spinal cord, lungs and esophagus. Equally spaced, 7-field IMRT-plans were designed using 6 or 10 MV photons and direct machine parameter optimization (Pinnacle, Philips, Best, the Netherlands) (24). The prescription-dose was specified at a representative point in the PTV. The dose distribution within 99% of the PTV was >90% and <115% of the prescribed dose.

Setup correction protocol

From January 2007 to December 2012 an off-line shrinking-action level setup correction protocol was used (25). In this protocol CBCT's were acquired during the first three fractions, using Elekta Synergy 4.6 (Elekta Oncology Systems Ltd., Crawley, UK) augmented with in-house developed software. If no correction was necessary

(average setup error over 3 fractions <5.2mm in each direction), then weekly CBCTs were acquired for the remainder of the treatment fractions. If a correction was executed, the shrinking action protocol restarted with three fractions including CBCT verification. This resulted in a minimum of 7 CBCT's per patient. Between January 2013 to December 2013 an online action protocol was used; where daily CBCT's were acquired, and a daily set-up correction was performed immediately before the start of radiation. The CBCT's were registered to the MidP-CT based on the vertebrae, carina and\or the primary tumor. The CBCT registrations were performed by at least two trained technicians.

Follow-up and endpoint definition

Primary endpoints were overall survival (OS), progression free survival (PFS) and local regional control (LRC). OS was calculated from the start of treatment until the last date of follow-up or death. PFS was calculated until the date of first progression (local, regional or distant) or last date of follow-up or death. LRC was calculated until the date when a recurrence occurred within the primary tumor or in the irradiated mediastinal lymph nodes region (outfield mediastinal recurrence was considered as progressive disease but not as local recurrence). Progressive disease was scored based on available clinical data or imaging report of tumor progression. After treatment, follow-up was performed every 3 months alternating between the pulmonologist and radiation oncologist. After 2 years, follow-up was performed every 6 months.

Deformable image registration and contouring

Since all CBCT's of all patients consisted of very much data, manual delineation was not possible. Therefore, the volume change of the GTV of the primary tumor was defined with deformable image registration (DIR). DIR is a process of defining a map with deformations between two images in a nonlinear way, providing a voxel to voxel mapping between 2 scans. One image is considered the fixed image (CBCT), and the other one the moving image (MidP-CT) (26-28). DIR was performed with in-house developed software (Match42). First a clip box was defined encompassing the PTV, in which the DIR of the MidP-CT to the CBCT was performed using a B-splines algorithm (29). The GTV of the MidP-CT was deformed onto the CBCT using the deformation vector field from the DIR. The GTV of the CBCT was subsequently extracted.

Statistical analysis

Baseline characteristics

Tumor and patient characteristics at baseline are presented as proportions, mean (+standard deviation (SD)) or median (+ interquartile range (IQR)) in case of a not normally distributed variable.

Quality of Deformable Registration

To test the reliability of the DIR, we performed a sensitivity analysis in 66 patients for whom we manually delineated the GTV of the primary tumor on the CBCTs of the first and last fraction and compared this with the deformable GTV. (These 66 patients were used in a pilot study, in which we delineated manually the GTVs on the CBCTs). The quality of the deformable GTVs was subsequently assessed based on the correlation between the manual and the deformable relative GTV using the Pearson correlation coefficient. Further, a Bland Altman plot was used to further investigate the agreement between the manual and the deformable relative GTV.

Latent Class Mixed Modelling

Latent Class Mixed Modelling (LCMM) was used to identify subgroups with distinct treatment responses (16-19), specifically, relative GTV-change during CCRT. LCMM assumes a heterogeneous population of subjects with each subgroup having a specific average profile of the longitudinal marker. The GTV on the MidP-CT was regarded as baseline volume (100%) and the relative volume compared to baseline was calculated at each CBCT. To best reflect the shape of trajectories observed within the data and the distribution of GTV-change, a class-specific quadratic trajectory over time was assumed and a normalization of GTV-change was simultaneously done by splines (quadratic I-splines with 3 internal knots placed at the quantiles). Intra-patient correlation was captured by correlated individual Gaussian random effects on the intercept, time and time squared. To determine the optimal number of subgroups, a stepwise forward approach was used. First, a model with one subgroup was constructed (one average trajectory applying for all patients), and step by step, an additional subgroup, with a conceivably distinct trajectory from the already identified subgroups was added. For each model, a grid of initial values (20 departures) was also considered to ensure the convergence toward the global maximum. The optimal number of subgroups was chosen, based on a combination of (i) goodness-of-fit

with the lowest Bayesian Information Criterion (BIC) (where a difference of at least 10 points is regarded as a sufficient improvement), (ii) discriminatory power with the best mean posterior probabilities of class-membership (mean probability >0.80) and (iii) clinically relevant differences between the subgroups (where subgroups with <5% of patients were considered clinically irrelevant). The Grolts-checklist was followed as much as possible to report on the LCMM (30).

Differences in baseline characteristics between the subgroups were tested using Pearson Chi Square tests (categorical variables), Kruskal-Wallis tests (non-parametric and >2 groups) or ANOVA (parametric and >2 groups).

To test the potential benefit of adding tumor response to a baseline prediction model, we compared the baseline model and the baseline+LCMM tumor-volume change model using the Harrell's c-statistic.

Sensitivity analyses

To validate current literature (13-15) on the prognostic potential of GTV changes during treatment, we performed supplementary analyses in which similar definitions, as used in this literature, of relative tumor volume change between first and last fraction were considered:

$$\text{rel\_GTVfirst} - \text{last} = 100 * (GTV fraction 1 - GTV\ last\ fraction)/(GTV\ fraction\ 1)$$ (14).

(In patients for whom no CBCT was available of the last fraction, the CBCT made in the last week was used.)

And the relative tumor volume change of the GTV between fraction 11 and 21:

$$\text{rel\_GTV}11 - 21 = 100 * (GTV fraction 11 - GTV fraction\ 21)/(GTV fraction\ 11)$$ (15).

To replicate the analyses done in the literature, these relative changes were then dichotomized according to the median value of the group and the association with treatment outcome was subsequently tested using Cox regression analyses. Multivariate cox regression analyses were then performed to investigate the independent association of the GTV-change parameters with OS, PFS and LRC. Furthermore, univariate cox regression analyses were performed to associate the median cut-off values from literature with treatment outcome, namely; 39.3 % (rel_$GTV_{first-last}$) and 22.8% (rel_GTV_{11-21}) (14, 15). Finally, the influence of pathology was also assessed by stratifying for; AC or SCC and NSCLC-not otherwise specified (NOS) (13).

Baseline analyses and cox proportional hazard analyses were performed in SPSS version 22.0 for Windows. LCMM was performed in R version 3.4.1. with package LCMM (lcmm function)(31). A p-value of ≤ 0.05 was regarded as statistically significant.

Results

In this study, 394 patients were included. Patient and tumor characteristics are shown in **Table 1.** The median follow-up was 63 months (IQR 48-83), median OS was 23 months (IQR 11-67), median PFS was 17 months (IQR 7-66) and the median LRC was 63 months (IQR 17-NA) (**Supplement Figure 1**). In total, 288 patients died (73.1%) before the end of study of whom 221 (56.1%) had lung cancer related mortality. Progressive disease was observed for 259 patients (66%) of whom 113 (29%) had local or regional infield recurrence.

The Pearson correlation coefficient between the manually delineated GTV and the deformable GTV was very high, 0.978 (p=0.001) for the first fraction and 0.951 (p=0.001) for the last CBCT, respectively. The Bland Altman plot (**Supplement Figure 2**) further showed a good agreement (B-value of 0.008 (p=0.767)) for the first fraction and 0.037 (p=0.393) for the last CBCT, respectively).

In general, the majority of patients (93%) had tumor volume reduction of the primary tumor during treatment (**Figure 1**). Seven percent (N=26) of the patients showed a stable volume or progression during treatment. Using LCMM, 3 subgroups with distinct trajectories of relative GTV-change during CCRT were identified (**Figure 2**). Addition of a 4th subgroup did not result in an improvement of fit, included a subgroup containing only 12 patients (3%), and was therefore considered clinically irrelevant. The first, and largest subgroup showed limited progression between the MidP-CT and start of treatment and showed limited tumor volume reduction during CCRT (subgroup 1, N=327, 83%), the second subgroup showed more progression between MidP-CT and start of treatment and a more profound tumor reduction during CCRT (subgroup 2, N=39, 10%). The third subgroup showed the most progression between MidP-CT and start, followed by the steepest tumor volume reduction during CCRT (subgroup 3, N=28, 7%).

Subgroup 1 and 2 contained significantly more males compared to subgroup 3 (p=0.014) (**Table 1**). No significant differences in other patient and tumor characteristics were observed. Although not significant, a tendency towards a higher

median GTV-volume at baseline and a lower proportion of adenocarcinomas was seen in subgroup 3.

In multivariate Cox analyses, WHO-PS (HR:2.93), age (HR:1.56) and GTV-volume of the primary tumor (HR:1.42) were significantly associated with OS, and WHO-PS (HR:2.12), nodal-stage (HR:1.85) and GTV-volume of the primary tumor (HR:1.47) were significantly associated with PFS (**Table 2**). Surprisingly none of GTV-change parameters were significantly associated with treatment outcome. When the 3-subgroup classification derived from LCMM was added to the multivariate baseline model for OS, the Harrell's c-statistic did not substantially change (baselinemodel c-statistics = 0.624; baselinemodel+ LCMM subgroup c-statistics = 0.628). Kaplan Meier plots of OS, PFS and LRC of the subgroups are shown in **Supplement Figure 3**.

In our cohort, the median decrease of tumor volume was 18.5% (IQR 8.9 - 32.5) for $rel\_GTV_{first\text{-}last}$ and 11.9% (IQR 4.4-18.2) for $rel\_GTV_{11\ -21.}$ No significant different OS, PFS and LRC rates were found for $rel\_GTV_{first\text{-}last}$ or_ $rel\_GTV_{11\text{-}21}$ (**Table 2**).

Median cut-off values of tumor volume change from literature were higher; 39.3% (22) and 22.8% (23), respectively. Nonetheless, no significant OS differences were found for those cut-off values either (HR: 1.10, p-value 0.571 & HR: 1.32, p-value 0.227 respectively).

Within the pathology subgroup analysis a borderline significant association was found only for $rel\_GTV_{first\text{-}last}$ in the AC-subgroup (HR:1.50, p-value:0.064). None of the other GTV-change parameters were significantly associated with OS, PFS or LRC in either subgroup (**Table 3**).

Table 1: patient and tumor characteristics from the total group and the 3 subgroup model identified by Latent Class Growth Modelling.

Patient and tumor characteristics	N=394 Total N (%)	N=327 Subgroup 1 N (%)	N=39 Subgroup 2 N (%)	N=28 Subgroup 3 N (%)	P-value
Sex					0.014
Male	233 (59.1%)	203 (62.1%)	20 (51.3%)	10 (35.7%)	
Female	161 (40.9%)	124 (37.9%)	19 (48.7%)	18 (64.3%)	
WHO performance status					0.152
0	137 (34.8%)	106 (32.4%)	18 (46.2%)	13 (46.4%)	
1	242 (61.4%)	209 (63.9%)	19 (48.7%)	14 (50%)	
2	15 (3.8%)	12 (3.7%)	2 (5.1%)	1 (3.6%)	
Stage					0.759
1&2	26 (6.6%)	26 (8.0%)	0 (0%)	0 (0%)	
3A	212 (53.8%)	166 (50.8%)	26 (66.7%)	20 (71.4%)	
3B	156 (39.6%)	135 (41.3%)	13 (33.3%)	8 (28.6%)	
Tumor-stage					0.199
Tx-T1	70 (17.8%)	57 (17.4%)	7 (17.9%)	6 (21.4%)	
T2	113 (28.7%)	88 (26.9%)	16 (41%)	9 (32.1%)	
T3	85 (21.6%)	71 (21.7%)	6 (15.4 %)	8 (28.6%)	
T4	126 (32%)	111 (33.9%)	10 (25.6%)	5 (17.9%)	
Nodal stage					0.315
N0-1	81 (20.6%)	74 (22.6%)	5 (12.8%)	2 (7.1%)	
N2	232 (58.9%)	186 (56.9%)	26 (66.7%)	20 (71.4%)	
N3	81 (20.6%)	67 (20.5%)	8 (20.5%)	6 (21.4%)	
Pathology					0.119
Adenocarcinoma	127 (32.2%)	104 (31.8%)	17 (43.6%)	6 (21.4%)	
Squamous cell carcinoma	132 (33.5%)	114 (34.9%)	10 (25.6%)	8 (28.6%)	
Non-small-cell lung cancer NOS	135 (34.3%)	109 (33.3%)	12 (30.8%)	14 (50%)	
GTV					0.669
Median GTV	77.1 cc	76.7 cc	75.3 cc	101.1 cc	
Age					0.314
Mean age	62 year	62 year	63 year	60 year	

Table 2: Univariate and multivariate Cox regression analysis for Overall Survival (OS), Progression Free Survival (PFS) and Local Regional Control (LRC). HR = Hazard Ratio, NOS = not otherwise specified, WHO PS: World Healthcare Organization Performance Score, GTV = Gross Tumor Volume, LCGM = Latent Class Growth Modelling. * GTV of the patients was ranked in 3 equal groups.

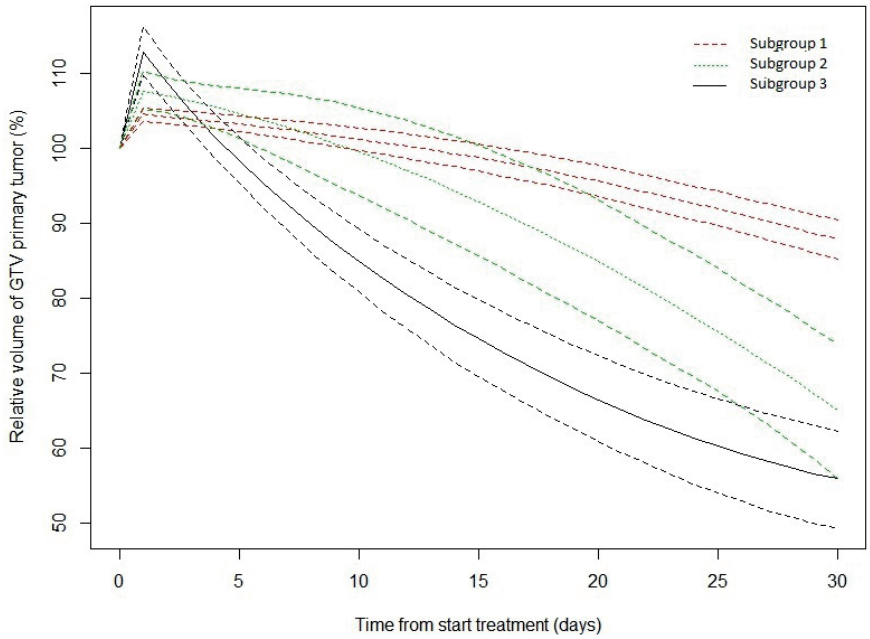
Variable	HR OS uni	P-value OS uni	HR OS multi	P-value OS multi	HR PFS uni	P-value PFS uni	HR PFS multi	P-value PFS multi	HR LRC uni	P-value LRC uni
Sex										
Male	1.000		1.000		1.000				1.000	
Female	0.695	***0.003***	0.790	0.063	0.850	0.198			0.895	0.561
Age										
≤62	1.000		1.000		1.000				1.000	
62<	0.638	***0.001***	1.560	***0.001***	1.216	0.118			1.320	0.145
WHO PS										
WHO PS 0	1.000		1.000		1.000		1.000		1.000	
WHO PS 1	1.374	***0.015***	1.258	0.085	1.249	0.096	1.286	0.065	1.349	0.139
WHO PS 2	2.911	***0.001***	2.933	***0.001***	2.069	***0.039***	2.120	***0.036***	1.798	0.330
Pathology										
Adenoca	1.000		1.000		1.000				1.000	
Squamousca	1.521	***0.004***	1.315	0.071	1.000	1.000			1.212	0.395
NSCLC NOS	1.130	0.414	1.085	0.592	0.932	0.644			0.845	0.479
Thoracic stage										
Stage I&II	1.000				1.000				1.000	
Stage IIIA	1.346	0.272			1.238	0.433			0.888	0.741
Stage IIIB	1.526	0.123			1.514	0.132			1.164	0.676
T-stadium										
Tx-1	1.000				1.000				1.000	
T2	1.095	0.619			1.421	0.069			2.026	***0.019***
T3	1.153	0.464			1.415	0.092			1.544	0.191
T4	1.251	0.208			1.316	0.157			1.466	0.220
N-stage										
N0-1	1.000				1.000		1.000		1.000	
N2	1.256	0.147			1.274	0.141	1.412	***0.040***	1.036	0.878
N3	1.409	0.068			1.553	***0.024***	1.847	***0.002***	1.378	0.259
GTV primary*										
GTV-small	1.000		1.000		1.000		1.000		1.000	
GTV-intermediate	1.268	0.107	1.181	0.271	1.145	0.379	1.232	0.183	1.157	0.518
GTV-large	1.505	***0.005***	1.424	**0.019**	1.430	***0.019***	1.474	***0.013***	1.184	0.476
3 subgroup model LCMM										
Subgroup 1	1.000				1.000				1.000	
Subgroup 2	1.111	0.592			1.131	0.555			1.188	0.626
Subgroup 3	1.020	0.934			0.950	0.839			0.810	0.649

Variable	HR OS uni	P-value	HR OS multi	P-value	HR PFS uni	P-value	HR PFS multi	P-value	HR LRC uni	P-value
rel_GTV-first-last										
≤median	1.000				1.000				1.000	
>median	1.084	0.515			1.058	0.662			0.961	0.840
rel_GTV11-21										
≤median	1.000				1.000				1.000	
>median	1.231	0.163			1.142	0.438			1.010	0.967

Table 3: Univariate and multivariate Cox regression analysis for Overall Survival (OS) for the subgroup analysis (adenocarcinoma (AC), squamous cell carcinoma (SCC) and NSCLC-not otherwise specified (NOS)). HR = Hazard Ratio, WHO PS: World Healthcare Organization Performance Score, GTV = Gross Tumor Volume LCGM = Latent Class Growth Modelling. * GTV of the patients was ranked in 3 equal groups.

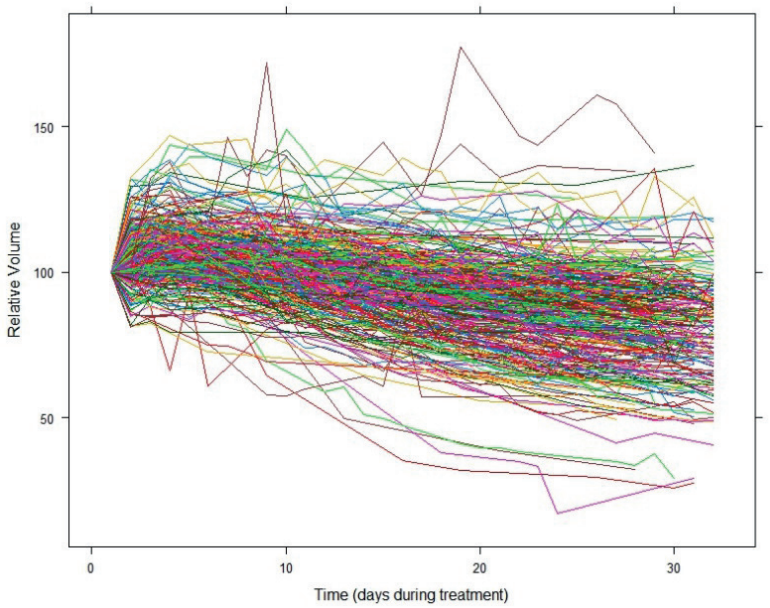
Variable	HR (OS AC) uni	P-value	HR (OS AC) multi	P-value	HR (OS SCC) uni	P-value	HR (OS SCC) multi	P-value	HR (OS NOS) uni	P-value	HR (OS NOS) multi	P-value
Sex												
Male	1.000				1.000				1.000			
Female	0.740	0.168			0.786	0.280			0.714	0.111		
Age												
≤62	1.000				1.000		1.000		1.000			
62<	1.421	0.110			1.745	***0.008***	1.860	***0.004***	1.349	0.148		
WHO												
WHO PS 0	1.000				1.000				1.000		1.000	
WHO PS 1	1.052	0.828			1.244	0.349			1.535	***0.053***	1.535	***0.053***
WHO PS 2	0.946	0.927			1.926	0.377			8.936	***0.000***	8.936	***0.000***
Stage												
Stage I&II	1.000				1.000				1.000			
Stage IIIA	4.044	***0.053***			0.761	0.525			1.098	0.817		
Stage IIIB	4.028	***0.056***			0.978	0.959			1.254	0.583		
T-stage												
Tx-1	1.000				1.000				1.000			
T2	0.963	0.899			0.851	0.661			1.219	0.519		
T3	0.938	0.854			0.435	0.417			1.520	0.183		
T4	0.913	0.782			0.998	0.996			1.267	0.417		
N-stage												
N0-1	1.000		1.000		1.000		1.000		1.000			
N2	2.467	***0.025***	2.467	***0.025***	1.078	0.749	1.081	0.739	1.212	0.466		
N3	2.452	***0.044***	2.452	***0.044***	2.050	**0.018**	2.273	**0.007**	1.222	0.515		
GTV primary*												
GTV-small	1.000				1.000				1.000			
GTV-intermediate	1.028	0.917			1.151	0.604			1.282	0.336		
GTV-large	1.260	0.389			1.453	0.184			1.407	0.161		

Variable	HR (OS AC) uni	P-value	HR (OS AC) multi	P-value	HR (OS SCC) uni	P-value	HR (OS SCC) multi	P-value	HR (OS NOS) uni	P-value	HR (OS NOS) multi	P-value
3 subgroup model LCMM												
Subgroup 1	1.000				1.000				1.000			
Subgroup 2	1.256	0.467			1.124	0.737			1.109	0.782		
Subgroup 3	1.416	0.557			0.919	0.841			0.990	0.976		
rel_GTV-first-last												
≤median	1.000				1.000				1.000			
>median	1.503	**0.064**			0.989	0.953			0.943	0.773		
rel_GTV 11-21												
≤median	1.000				1.000				1.000			
>median	1.794	0.110			1.577	0.338			1.311	0.471		

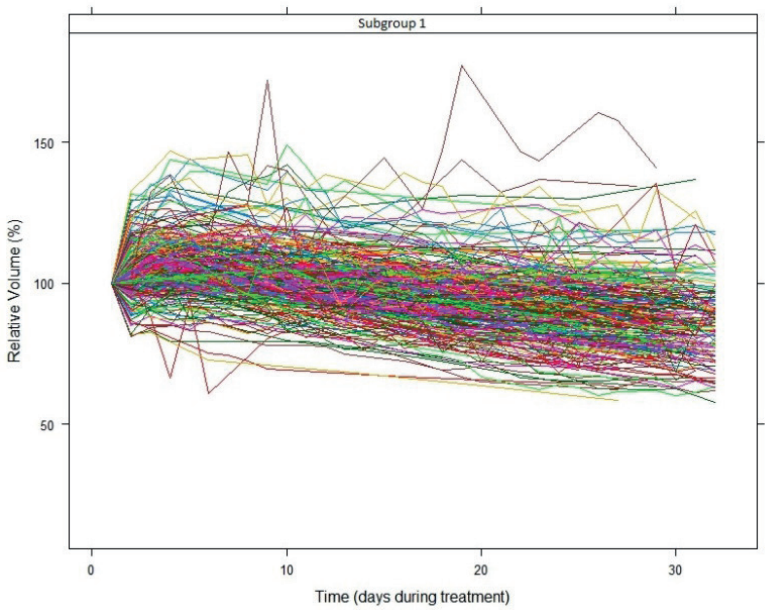


▲**Figure 1:** Distinct relative tumor volume change trajectories during concurrent chemoradiation treatment for NSCLC patients identified with Latent Class Mixed Modelling. Subgroup 1 (red, N=327), subgroup 2 (green, N=39), subgroup 3 (black, N=28). Time=0 is the date of the RTplanning-CT and time =1 is the first date of the treatment. The GTV-change between time=0 and time =1 is the progression of the GTV between RTplanning-CT and start of treatment. The dashed lines show the 95%CI.

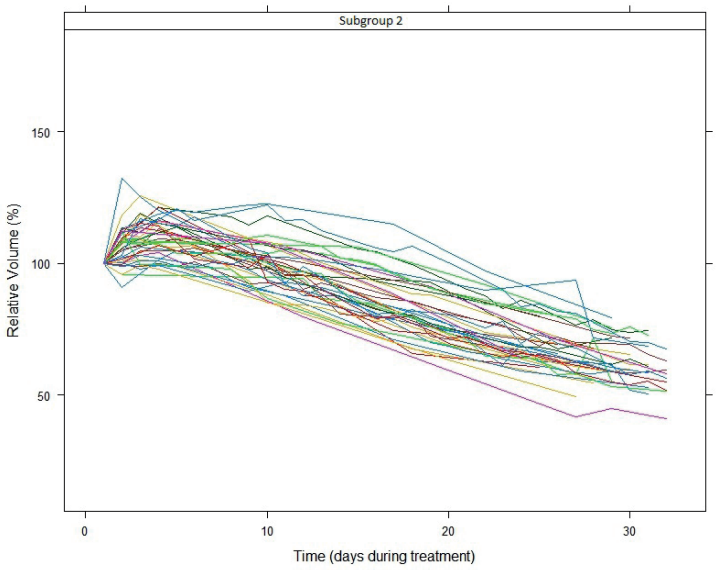
A


Relative Volume
150
100
50
0
10
20
30
Time (days during treatment)

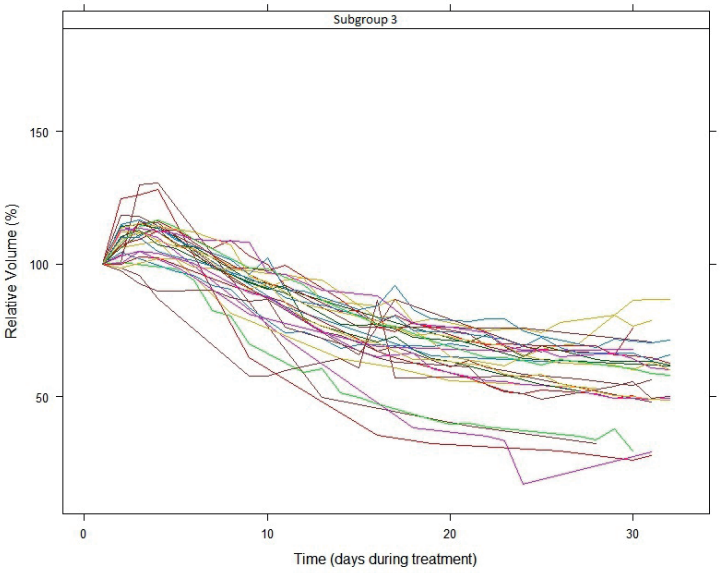
B


Subgroup 1
Relative Volume (%)
150
100
50
0
10
20
30
Time (days during treatment)

C



D



▲**Figure 2:** (A) Individual observed trajectories of GTV volume change for the total cohort (N= 394). (B) Individual observed trajectories of GTV volume change for subgroup 1(N= 327). (C) Individual observed trajectories of GTV volume change for subgroup 2 (N= 39). (D) Individual observed trajectories of GTV volume change for subgroup 1(N= 28). Day 0 is planning CT scan of the radiotherapy (100%).

Discussion

In this study, we identified 3 subgroups with distinct GTV-changes during treatment. The identified subgroups each showed an increasingly steep volume reduction during CCRT. However, no associations of membership of a particular subgroup with outcomes were observed.

Recent literature (13-15) suggested associations between tumor volume change and OS. In our present study, we could not validate any of the published associations of tumor volume changes and OS, either by considering Latent Class Mixed Modelling or by replicating the original analyses. An explanation for this might be that these previous studies of Brink et al.(13) Jabbour et al.(14) and Wald et al.(15) were very small studies (99, 38 and 52 patients, respectively). As Wald et.al.(15, 32) already emphasized, those studies can only be considered as hypothesis generating rather than conclusive. Since our large study could not validate these results, the observed association could be clarified due to a power problem in those smaller studies (13-15).

In coherence with previous studies (4-11), a large baseline GTV of the primary tumor remained a significant predictor for worse OS and PFS. This remained not significant in the pathology subgroup analysis, probably due to a power problem, but the same tendency in the strength of association was observed. Although we identified 3 different subgroups with distinct volume changes, most patients (83%) were grouped into the same subgroup with limited tumor volume regression during treatment. When looking at the individual patterns of treatment response (Figure1), one might acknowledge that the assumption of heterogeneity in treatment response could not be confirmed. Moreover, Wald et al.(32) did not observe heterogeneity in treatment response either. Therefore, the addition of longitudinal data of tumor volume change during treatment might not improve the current risk models based on baseline information (4-11). Nevertheless, using longitudinal parameters to improve the predictive accuracy of outcome models are an important topic of ongoing research (33-35). Novel longitudinal parameters such as imaging features, circulating tumor DNA and molecular tumor profiling might be relevant in developing more accurate dynamic prediction models for a more personalized treatment and follow-up care approach.

The median GTV-volume at start of treatment was comparable to the median GTV published in literature (13-15), however we observed a lower GTV-volume reduction compared to other studies (13-15). The reason for this might be our reduced overall treatment time (OTT), since patient were treated with a hypofractionated CCRT regime with an OTT of 32 days (24x2.75Gy) compared to an OTT between 40-51 days (60-74 Gy in 1.8-2Gy/fraction)) in the literature(13-15). Furthermore, different chemotherapy regimens were used. In our institute, daily low-dose Cisplatin is administered as a radio sensitizer, while conventionally weekly or three weekly administrations of high dose chemotherapy are applied and sometimes combined with induction chemotherapy. Moreover, different chemotherapy regimens, radiotherapy-schedules and OTT could have influenced the onset of the DNA damage response system (36, 37). The DNA damage response system determines the radio sensitivity, type and timing of cell death. The vast majority of proliferating tumor cells die at a relatively long interval after irradiation, usually after attempting mitosis 1 or 2 times. Therefore, this could have affect the GTV- change, which could explain the observed differences.

In patients with AC and more than the median GTV-change, a tendency towards a worse OS compared to other pathology groups was found. In the LCMM subgroups, the same tendency in association was found; subgroup 3 (the subgroup with the sharpest decrease in volume) showed worse OS compared to the other subgroups. However, this was not statistically significant, probably due to the small number of patients in this subgroup (N=6). This association is in accordance with the study of Brink et al.(13), who found that patients with more GTV-change during treatment showed worse treatment outcomes. Treatment guidelines for CCRT for LA-NSCLC patients are currently based on 'one-size-fits-all' standards and there is no risk based distinction on pathology. Previously published literature already reported higher incidences of brain metastases in AC (38-41), a higher incidence of distant metastases in AC and that loco regional failures are more common in SCC (11), underlining that AC and SCC might be two different entities. A possible explanation could be that more aggressive tumors have a higher mitotic rate and are therefore more radiosensitive tumors, resulting in increased tumor regression during treatment. This is comparable to small-cell lung cancer, which is in general very radiosensitive due to the higher mitotic count (rapid growth) and has a poor treatment outcome (42). Therefore, response monitoring during treatment within adenocarcinoma patients might be beneficial and further investigation is needed.

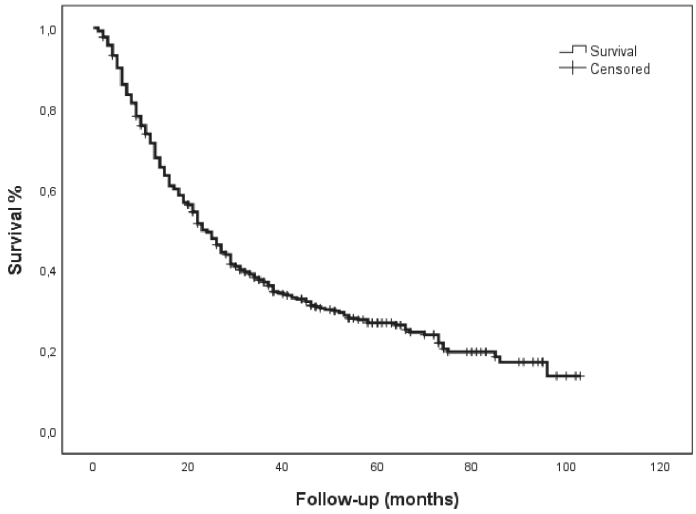
To conclude, 3 different subgroups of GTV-volume change during treatment were identified with LCMM**.** In contrast with previous results, suggesting an association between GTV-change and overall survival, membership of a distinct subgroup of GTV-change during treatment did not result in different risks of outcomes whereas baseline GTV of the primary tumor was significantly associated with OS. Therefore, risk stratification at baseline might already be accurate enough in identifying the best treatment strategy for most patients. In patients with adenocarcinoma, and a steep decrease of GTV during treatment did show a tendency towards a worse OS.

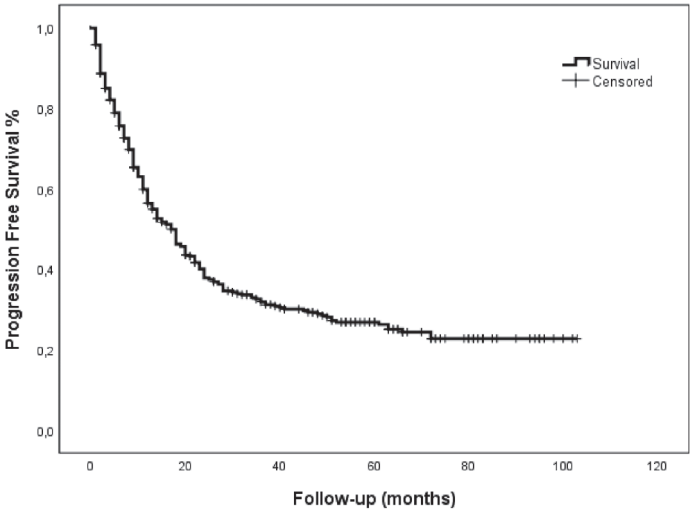
Reference

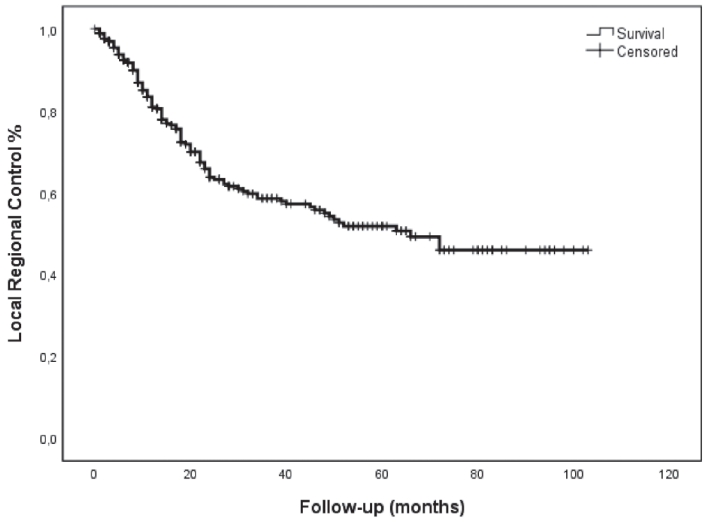
1. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.
2. Dieleman EMT, Uitterhoeve ALJ, van Hoek MW, van Os RM, Wiersma J, Koolen MGJ, et al. Concurrent daily Cisplatin and high dose radiotherapy in patients with stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2018.
3. Walraven I, van den Heuvel M, van Diessen J, Schaake E, Uyterlinde W, Aerts J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Radiother Oncol. 2016;118(3):442-6.
4. Warner A, Dahele M, Hu B, Palma DA, Senan S, Oberije C, et al. Factors Associated With Early Mortality in Patients Treated With Concurrent Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016;94(3):612-20.
5. Jochems A, Deist TM, El Naqa I, Kessler M, Mayo C, Reeves J, et al. Developing and Validating a Survival Prediction Model for NSCLC Patients Through Distributed Learning Across 3 Countries. Int J Radiat Oncol Biol Phys. 2017;99(2):344-52.
6. Driessen EJ, Bootsma GP, Hendriks LE, van den Berkmortel FW, Bogaarts BA, van Loon JG, et al. Stage III Non-Small Cell Lung Cancer in the elderly: Patient characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. Radiother Oncol. 2016;121(1):26-31.
7. Carvalho S, Troost EG, Bons J, Menheere P, Lambin P, Oberije C. Prognostic value of blood-biomarkers related to hypoxia, inflammation, immune response and tumour load in non-small cell lung cancer - A survival model with external validation. Radiother Oncol. 2016;119(3):487-94.
8. 8Lambin P, Zindler J, Vanneste BG, De Voorde LV, Eekers D, Compter I, et al. Decision support systems for personalized and participative radiation oncology. Adv Drug Deliv Rev. 2017;109:131-53.
9. van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential analysis of local and regional failure in locally advanced non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Radiother Oncol. 2016;118(3):447-52.
10. Oberije C, De Ruysscher D, Houben R, van de Heuvel M, Uyterlinde W, Deasy JO, et al. A Validated Prediction Model for Overall Survival From Stage III Non-Small Cell Lung Cancer: Toward Survival Prediction for Individual Patients. Int J Radiat Oncol Biol Phys. 2015;92(4):935-44.
11. Nygard L, Vogelius IR, Fischer BM, Kjaer A, Langer SW, Aznar MC, et al. A Competing Risk Model of First Failure Site after Definitive Chemoradiation Therapy for Locally Advanced Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(4):559-67.
12. Bral S, De Ridder M, Duchateau M, Gevaert T, Engels B, Schallier D, et al. Daily megavoltage computed tomography in lung cancer radiotherapy: correlation between volumetric changes and local outcome. Int J Radiat Oncol Biol Phys. 2011;80(5):1338-42.

13. Brink C, Bernchou U, Bertelsen A, Hansen O, Schytte T, Bentzen SM. Locoregional control of non-small cell lung cancer in relation to automated early assessment of tumor regression on cone beam computed tomography. Int J Radiat Oncol Biol Phys. 2014;89(4):916-23.
14. Jabbour SK, Kim S, Haider SA, Xu X, Wu A, Surakanti S, et al. Reduction in Tumor Volume by Cone Beam Computed Tomography Predicts Overall Survival in Non-Small Cell Lung Cancer Treated With Chemoradiation Therapy. Int J Radiat Oncol Biol Phys. 2015;92(3):627-33.
15. Wald P, Mo X, Barney C, Gunderson D, Haglund AK, Bazan J, et al. Prognostic Value of Primary Tumor Volume Changes on kV-CBCT during Definitive Chemoradiotherapy for Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2017;12(12):1779-87.
16. Walraven I, Kwint M, Belderbos J. The Additional Prognostic Value of Tumor Volume Changes during Chemoradiotherapy in Patients with Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(9):e181-e2.
17. Proust-Lima C, Sene M, Taylor JM, Jacqmin-Gadda H. Joint latent class models for longitudinal and time-to-event data: a review. Stat Methods Med Res. 2014;23(1):74-90.
18. Proust-Lima C, Taylor JM. Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of posttreatment PSA: a joint modeling approach. Biostatistics. 2009;10(3):535-49.
19. Twisk J, Hoekstra T. Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol. 2012;65(10):1078-87.
20. Walraven I, Mast MR, Hoekstra T, Jansen AP, van der Heijden AA, Rauh SP, et al. Distinct HbA1c trajectories in a type 2 diabetes cohort. Acta Diabetol. 2015;52(2):267-75.
21. Belderbos J, Sonke JJ. State-of-the-art lung cancer radiation therapy. Expert Rev Anticancer Ther. 2009;9(10):1353-63.
22. Wolthaus JW, Schneider C, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys. 2006;65(5):1560-71.
23. van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol. 2004;14(1):52-64.
24. Schwarz M, Alber M, Lebesque JV, Mijnheer BJ, Damen EM. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2005;62(2):561-70.
25. Bel A, Vos PH, Rodrigus PT, Creutzberg CL, Visser AG, Stroom JC, et al. High-precision prostate cancer irradiation by clinical application of an offline patient setup verification procedure, using portal imaging. Int J Radiat Oncol Biol Phys. 1996;35(2):321-32.
26. Sarrut D. Deformable registration for image-guided radiation therapy. Z Med Phys. 2006;16(4):285-97.
27. Guckenberger M, Baier K, Richter A, Wilbert J, Flentje M. Evolution of surface-based deformable image registration for adaptive radiotherapy of non-small cell lung cancer (NSCLC). Radiat Oncol. 2009;4:68.
28. Mencarelli A, van Kranen SR, Hamming-Vrieze O, van Beek S, Nico Rasch CR, van Herk M, et al. Deformable image registration for adaptive radiation therapy of head and neck cancer: accuracy and precision in the presence of tumor changes. Int J Radiat Oncol Biol Phys. 2014;90(3):680-7.

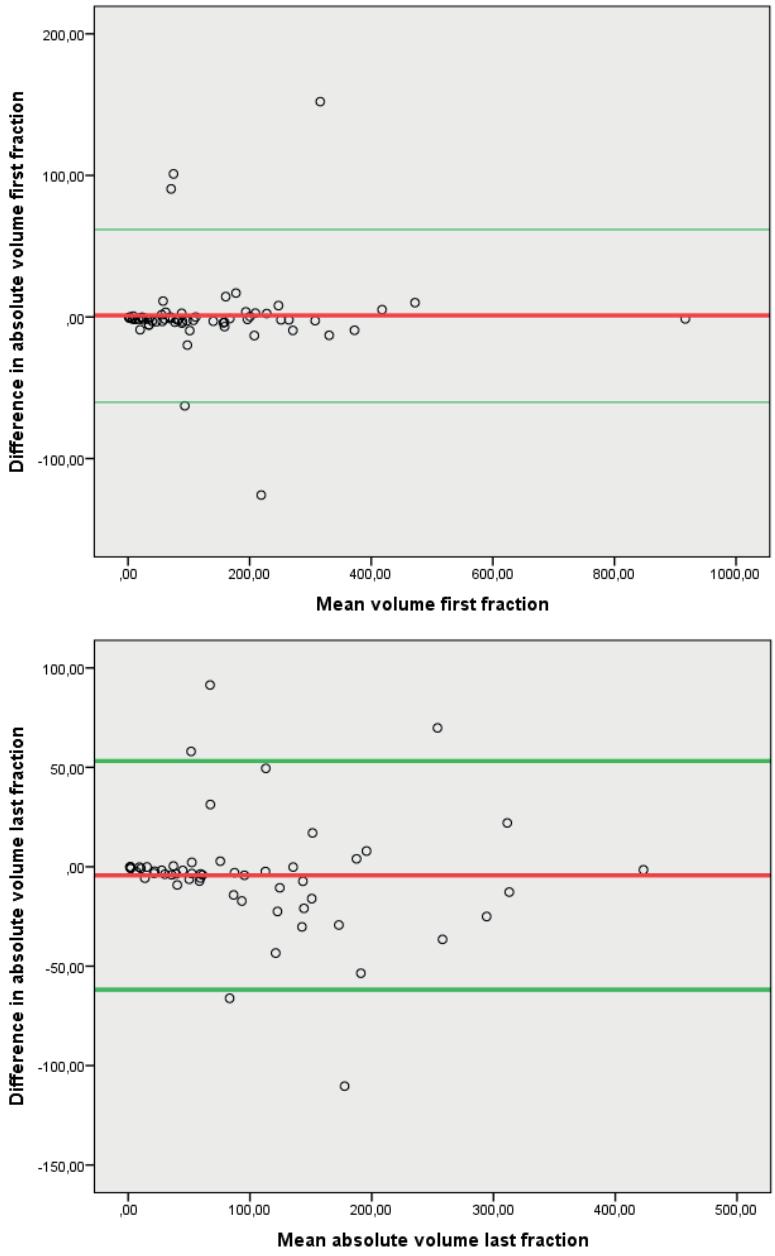
29. van Kranen S, Mencarelli A, van Beek S, Rasch C, van Herk M, Sonke JJ. Adaptive radiotherapy with an average anatomy model: evaluation and quantification of residual deformations in head and neck cancer patients. Radiother Oncol. 2013;109(3):463-8.
30. van de Schoot RS, M.; Winter, S.D.; Depaoli, S.;Vermunt, J.K.; . The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies. Structural Equation Modeling: A Multidisciplinary Journal. 2017 24: 451–467.
31. C. Proust-Lima, V. Philips, B. Liquet. Estimation of Extended Mixed Models Using Latent Classes and Latent Processes: The R Package lcmm. Journal of Statistical Software. 2017;78(2):1–56.
32. Mo X, Xu-Welliver M. Response to the Letter to Editor re: The Additional Prognostic Value of Tumor Volume Changes during Chemoradiotherapy in Patients with Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2018;13(9):e182-e3.
33. Bissonnette JP, Yap ML, Clarke K, Shessel A, Higgins J, Vines D, et al. Serial 4DCT/4DPET imaging to predict and monitor response for locally-advanced non-small cell lung cancer chemo-radiotherapy. Radiother Oncol. 2017.
34. van Timmeren JE, Leijenaar RTH, van Elmpt W, Reymen B, Oberije C, Monshouwer R, et al. Survival prediction of non-small cell lung cancer patients using radiomics analyses of cone-beam CT images. Radiother Oncol. 2017;123(3):363-9.
35. Paul J, Yang C, Wu H, Tai A, Dalah E, Zheng C, et al. Early Assessment of Treatment Responses During Radiation Therapy for Lung Cancer Using Quantitative Analysis of Daily Computed Tomography. Int J Radiat Oncol Biol Phys. 2017;98(2):463-72.
36. Forrester HB, Vidair CA, Albright N, Ling CC, Dewey WC. Using computerized video time lapse for quantifying cell death of X-irradiated rat embryo cells transfected with c-myc or c-Ha-ras. Cancer Res. 1999;59(4):931-9.
37. Begg AC, McNally NJ, Shrieve DC, Karcher H. A method to measure the duration of DNA synthesis and the potential doubling time from a single sample. Cytometry. 1985;6(6):620-6.
38. Earnest Ft, Ryu JH, Miller GM, Luetmer PH, Forstrom LA, Burnett OL, et al. Suspected non-small cell lung cancer: incidence of occult brain and skeletal metastases and effectiveness of imaging for detection--pilot study. Radiology. 1999;211(1):137-45.
39. Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ, et al. Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. J Clin Oncol. 2005;23(13):2955-61.
40. Na, II, Lee TH, Choe DH, Cheon GJ, Kim CH, Koh JS, et al. A diagnostic model to detect silent brain metastases in patients with non-small cell lung cancer. Eur J Cancer. 2008;44(16):2411-7.
41. Sanchez de Cos J, Sojo Gonzalez MA, Montero MV, Perez Calvo MC, Vicente MJ, Valle MH. Non-small cell lung cancer and silent brain metastasis. Survival and prognostic factors. Lung Cancer. 2009;63(1):140-5.
42. Fruh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi99-105.


Survival
Censored
Survival %
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
Follow-up (months)

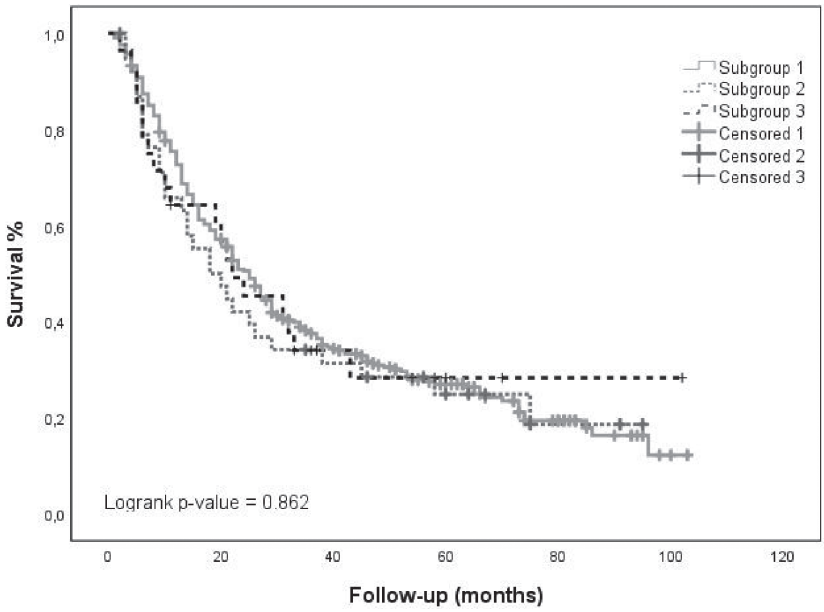

Survival
Censored
Progression Free Survival %
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
Follow-up (months)

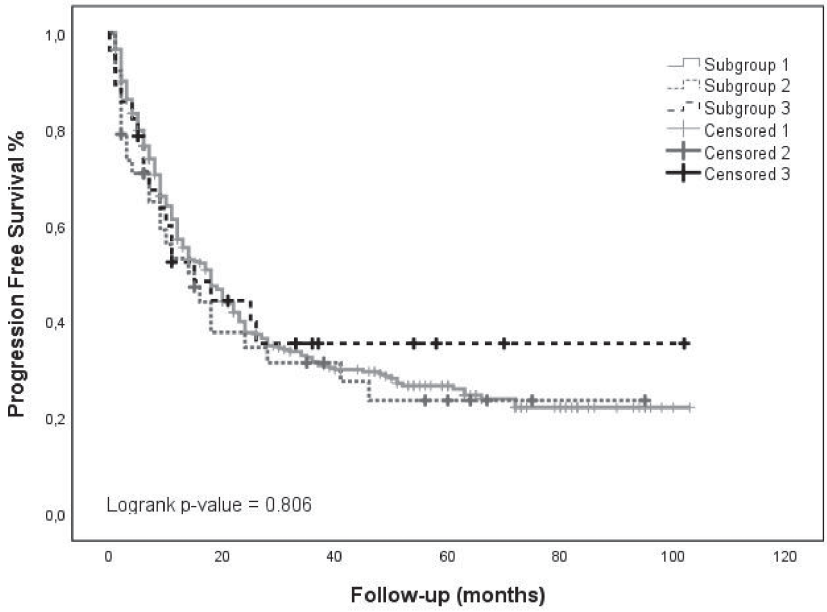


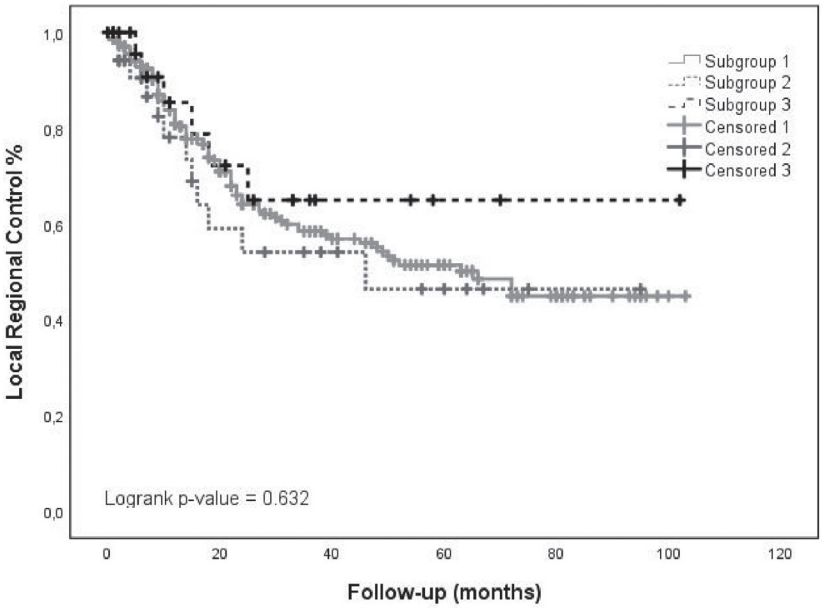
▲**Supp fig 1:** Kaplan Meier curves for Overall Survival, Progression Free Survival and Local Regional Control for the total cohort (N=394)



▲**Supp fig 2:** Bland Altman Plot: Plot of the difference against the mean of the absolute GTV volume by manually and deformable registration for the first and last CBCT.


Survival %
1,0
0,8
0,6
0,4
0,2
0,0
Subgroup 1
Subgroup 2
Subgroup 3
Censored 1
Censored 2
Censored 3
Logrank p-value = 0.862
0
20
40
60
80
100
120
Follow-up (months)


Progression Free Survival %
1,0
0,8
0,6
0,4
0,2
0,0
Subgroup 1
Subgroup 2
Subgroup 3
Censored 1
Censored 2
Censored 3
Logrank p-value = 0.806
0
20
40
60
80
100
120
Follow-up (months)



▲**Supp Fig 3**: Kaplan Meier curves for Overall Survival, Progression Free Survival and Local Regional Control for the 3 Subgroups identified with Latent Class Mixed Modelling. Subgroup 1 (N=327), subgroup 2 (N=39), subgroup 3 (N=28).

CHAPTER 6

ACUTE ESOPHAGUS TOXICITY IN LUNG CANCER PATIENTS AFTER INTENSITY MODULATED RADIATION THERAPY AND CONCURRENT CHEMOTHERAPY

Margriet Kwint., Wilma Uyterlinde, Chun Chen, Wilma Heemsbergen, Josien de Bois, Jan-Jakob Sonke, Michel van den Heuvel, Joost Knegjens, Marcel van Herk, José Belderbos

Int J Radiat Oncol Biol Phys. 2012;84(2):e223-e228. doi: 10.1016/j.ijrobp.2012.03.027

Purpose

The purpose of this study is to investigate the dose-effect-relation between acute esophageal toxicity (AET) and dose-volume-parameters of the esophagus after Intensity Modulated Radiotherapy (IMRT) and concurrent chemotherapy for Non-Small Cell Lung Cancer (NSCLC) patients.

Methods and materials

One hundred thirty nine inoperable NSCLC patients treated with IMRT and concurrent chemotherapy were prospectively analyzed. The fractionation scheme was 24 x 2.75 Gy. All patients received concurrent a daily dose Cisplatin (6 mg/m²). Maximum AET was scored according to CTC 3.0. Dose-volume-parameters V5 to V70, D_{mean} and D_{max} of the esophagus were calculated. A logistic regression analysis was performed to analyze the dose-effect relation between these parameters and grade ≥2 and grade ≥3 AET. The outcome was compared to the clinically used esophagus V35 prediction model for grade ≥2 after radical 3D conformal radiotherapy (3DCRT) treatment.

Results

In our patient group 9% did not develop AET, 31% developed grade 1, 38% grade 2 and 22% grade 3 AET. The incidence of grade 2 and 3 AET was not different compared to patients treated with CCRT using 3DCRT. The V50 turned out to be the most significant dosimetric predictor for grade ≥3 AET ($p=0.012$). The derived V50-model was shown to predict grade ≥2 significantly better compared to the clinical V35-model ($p<0.001$).

Conclusions

For NSCLC patients treated with IMRT and concurrent chemotherapy, the V50 was identified as most accurate predictor of grade ≥3 AET. There is no difference in the incidence of grade ≥2 AET between 3DCRT and IMRT in patients treated with concurrent chemoradiotherapy.

Introduction

Concurrent chemoradiotherapy (CCRT) has become the treatment of choice in locally advanced non-small cell lung cancer (NSCLC). A recent meta-analysis showed that for patients with NSCLC, treatment with CCRT significantly improved local control and survival compared to sequential chemoradiotherapy (SCRT) [1]. However, this is at the cost of more side-effects; CCRT results in more acute esophagus toxicity (AET) than RT-only or SCRT [2-7].

A part of the esophagus is often irradiated due to overlap with the planning target volume because of involvement of mediastinal lymph nodes or mediastinal tumor invasion. The mucosal layer of the esophagus is sensitive to irradiation induced damage [2-7]. Patients with insufficient intake due to radiation esophagitis are at risk for premature discontinuation of therapy. Predicting the risk of AET makes it possible to take appropriate precautions, such as individualized patient information, dietary guidance, hydration or tube feeding. Identifying the low-risk patients of AET gives the opportunity to escalate the dose of radiotherapy to improve tumor control.

Intensity Modulated Radiotherapy (IMRT) facilitates a more conformal dose distribution leading to increased organ sparing compared to 3D-conformal-radiotherapy (3DCRT) [8-10]. In a previous study, with mainly RT-only and SCRT treatments, we reported the V35 (relative volume of the esophagus receiving more than 35 Gy), as the best predictor of AET grade ≥2 after radical 3DCRT-treatment [2]. The treatment-planning esophagus constraint for 3DCRT at that time was length of the esophagus ≤12 cm and elective nodal irradiation was given [2]. In this historical dataset the incidence of grade 2 (54%) and grade 3 (27%) AET was higher in a subset of 37 patients treated with CCRT [2]. The derived V35 model was therefore scaled to cover the higher incidence of AET for CCRT, but due to the small sample size, evaluation of the best predictor for AET in CCRT was not feasible. Other studies revealed several dose-volume-parameters to predict AET [2-7]. One specific dose-volume-parameter was not designated yet as most reliable predictor of AET. All studies were based on 3DCRT. However, with IMRT dose-distributions and dose-volume-parameters for the esophagus have changed, which might reveal other predictors for AET.

The purpose of this study is to investigate the dose-effect-relation between acute esophagus toxicity and dose-volume-parameters of the esophagus after IMRT and concurrent chemoradiation for NSCLC patients.

Patients and methods

Patient selection

Between January 2008 and November 2010, patients with locally advanced NSCLC treated with CCRT in our institute were prospectively followed. Inclusion criteria for this study were treatment with CCRT, histology or cytology proven NSCLC, WHO≤2, adequate renal and hepatic functions and life expectancy >6 months. The clinical AET grades as well as the dose-volume-parameters of the esophagus were available for all patients. Former studies reported different dosimetric predictors for AET for SCRT and RT-only, compared to CCRT [6,7]. Therefore only patients were selected who received at least 50% of the planned chemotherapy dose and 100% of the radiotherapy dose.

All patients were treated with IMRT of 66 Gy in 24 fractions, once daily, 5 times per week. The concurrent chemotherapy regimen consisted of daily low dose Cisplatin intravenous (6 mg/m²) 1-2h before irradiation.

Radiotherapy preparation

For all patients a 3D-midventilation-CT (MidV-CT) was selected out of a respiration correlated 4DCT, in which the moving tumor was closest to its time-averaged mean position [11]. The gross tumor volume (GTV) and all pathological lymph nodes were delineated on the MidV-CT which was also registered with a recent fludeoxyglucose-positron-emission-tomography-(FDG-PET)-scan. Delineations were discussed in a multidisciplinary meeting. The GTV was expanded to a planning target volume (PTV) using margins of 12 mm +¼ of the 4DCT peak-to-peak tumor amplitude in orthogonal directions. For the lymph nodes a uniform PTV margin of 12 mm was used [12].

Critical organs were delineated according to a written protocol: heart, spinal cord, lungs and esophagus (from cricoïd to gastro-esophageal-junction). The planning-constraints used for the organs at risk were; esophagus V35<65%, mean lung-dose ≤20 Gy, spinal cord ≤50 Gy, total heart ≤40 Gy and of the heart ≤50 Gy and of the heart ≤66 Gy. Equally spaced, 7-field IMRT-plans were calculated using 10 or 6 MV photons and direct machine parameter optimization in the homo-lateral lung (Pinnacle version 9.0, Philips, Best, the Netherlands) [10]. The prescription-dose was specified at a representative point in the PTV. The dose inhomogeneity within the PTV was >90% and <115%.

Scoring of acute esophagus toxicity

AET was scored using the Common Toxicity Criteria 3.0 from start of treatment, until 3 months after. Grade 2 was scored in case of symptomatic and altered eating and intravenous fluids indicated for a period shorter than 24 hrs. Grade 3 included symptomatic and severely altered eating/swallowing and intravenous fluids, tube feedings, or total parenteral nutrition indicated ≥24 hrs; and grade 4 included life-threatening consequences. The patients were examined and toxicity was scored at baseline and weekly during treatment, until 3 weeks after treatment by the treating physician. Thereafter the patients were followed with 2 months intervals or more frequently if indicated. All patients consulted a dietician at least twice during treatment.

Dosimetric analysis

The physical RT-dose was converted to Normalized Total Dose (NTD) for 2 Gy per fraction with an α/β-ratio of 10 Gy for acute toxicity. With the NTD corrected dose, esophageal dose-volume-histograms (DVH) were computed and dose-volume-parameters were derived in steps of 5 Gy from V5 to V70, as well as the D_{mean} and D_{max}. For comparison with 3DCRT, DVH parameters of the current study using IMRT were compared to the data of 36 of the 37 patients treated with CCRT in the historical dataset (data for 1 patient was missing) [2].

Statistical analysis

To evaluate the introduction of IMRT in the CCRT-protocol, we compared the incidence of grade 2 and 3 AET with the historical patient data [2] using a chi-squared test.

The statistical analysis of AET predictability was performed in two steps. First, the V5-V70, D_{mean} and D_{max} were analyzed for correlation with the AET grade using Spearman's rank correlation coefficients. In the second step, the best dosimetric predictors for grade ≥2 and ≥3 AET were estimated, using a stepwise logistic regression method. The stepwise regression was done in a forward selection fashion, which involves starting with all candidate variables and testing them one by one for statistical significance, deleting variables that were least significant until the best predictor remained. The resulting logistic function is expressed as:

$$\text{AET Grade probability} = \frac{1}{1+\exp-(\beta_0 + \beta_1 Vx)}$$

Where β_0 and β_1 are the estimated coefficients and Vx is the most significant dosimetric parameter. The new model was then compared with the currently used constraint of the V35 [2] using chi-square distribution with 3 degrees of freedom (β_0, β_1, Vx) . The dose-volume-parameters of the current IMRT-patients were compared to the historical 3DCRT-data using a 2-sided student t-test. The data was analyzed by SPSS for Windows software, release 15.0 and graphs were generated by Matlab for Windows software, release R2009a.

Results

Patients

Between January 2008 and November 2010, 139 consecutive NSCLC patients treated with IMRT and concurrent chemotherapy were selected (**Table 1**). Median age was 63 years (range 38-85 years). A total of 109 (78%) patients received all 24 doses of chemotherapy. Due to decreasing renal function (N=20), gastro-intestinal (N=6), hematological (N=2) or cardiovascular (N=2) side effects, the Cisplatin stopped early after 13 up to 23 administrations (mean 19) in 22% of the patients.

From the 139 patients the incidences of AET were, 12 (9%), 43 (31%), 53 (38%) and 31 (22%) for grade 0, 1, 2 and 3 AET respectively. No grade 4 and 5 AET was observed. In analogy to the historical data, current AET was increased compared to the historical data for RT-only and SCRT [2] ($p<0.0002$). The current incidences using IMRT were not significantly different from the historical CCRT data with 3DCRT-treatment ($p=0.4832$ for AET grade ≥2 and $p=0.5457$ for AET grade ≥3).

Dosimetric variables

With the use of IMRT the relative volume of the esophagus receiving dose levels ranging from 5–40 Gy were significantly lower compared to 3DCRT, while the volume receiving 70 Gy was significantly increased (**Figure 1**).

The esophageal V65 turns out to have the highest correlation with AET with a correlation coefficient of 0.300 ($p<0.001$), although V25-V70, D_{max} and D_{mean} all significantly correlated with AET (**Table 2**). Additionally, correlations between dosimetric variables (e.g. with V50 shown in **Table 2**) indicate high mutual correlation with each other. This indicates that a wide range of dose-volume-parameters are

predictive of AET. For this reason, in building the logistic model, we only selected the most significant parameter to predict grade ≥2 and ≥3 AET, as can be achieved with the forward conditional selection logistic regression method. For prediction of grade 3 AET, the V50 was shown to be the most significant (p=0.013) parameter with a β_0 of -2.486 and a β_1 of 0.032 **(Table 3)**. For grade 2 AET, the D_{max} was the remaining parameter after forward selection. However, we expect that using D_{max} in the plan optimization will not sufficiently influence the dose distributions. Since grade 3 AET is clinically more relevant, and also for practical reasons, we also estimated the binary logistic regression parameters for grade 2 AET using the V50, which was also shown to be highly significant (p=0.012) (**Table 3**). Doing so, we establish one single parameter, which can be used to predict the probability of both grade ≥2 AET and grade ≥3 AET. The probability of developing acute esophagitis grade ≥3 can now be estimated using:

$$\text{AET grade 3 probability} = \frac{1}{1+\exp-(-2.486+0.032V_{50})}$$

and for grade 2 AET:

$$\text{AET grade} \geq 2 \text{ probability} = \frac{1}{1+\exp-(-0.515+0.027V_{50})}$$

The sigmoid shaped relationship between AET grade ≥2 and ≥3 and the V50 is plotted in **Figure 2**, together with the actual incidences of AET.

To illustrate the need to replace our current V35-model for grade ≥2 AET, we have plotted the actual V35 data of the current study with respect to the model (**Figure 3**). The log-likelihood difference between the V35 data estimated with the old model and the V50 data estimated with the new model corresponded to a significant difference with a p-value of 0.011 (chi-square distribution with 3 degrees of freedom), indicating superiority of the V50 model.

Using the Mann-Whitney test, patients experiencing grade 3 AET and receiving all planned doses of Cisplatin (26%) were compared to patients in whom Cisplatin was discontinued early (10%). This incidence was not significant different (p= 0.083).

Table 1: Patients Characteristics (NSCLC = non-small cell lung carcinoma; WHO = World Health Organization)

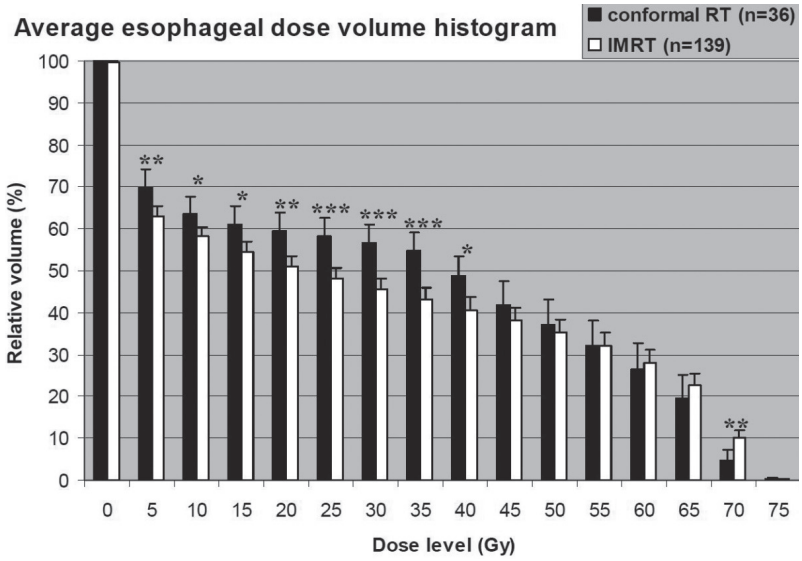
Characteristic	No. of patients (N=139)	%
Sex		
Male	84	60.4
Female	55	39.6
Stage		
IB	1	0.7
IIA	4	2.9
IIB	6	4.3
IIIA	82	59.0
IIIB	36	25.9
Recurrent NSCLC	10	7.2
Histology		
Squamous	47	33.8
Adenocarcinoma	29	20.9
Large cell/not specified	63	45.3
WHO		
0	14	10.1
1	101	72.7
2	24	17.3
Smoking during treatment		
Yes	87	62.6
No	52	37.4
Weight loss ≥5% last 6 months		
Yes	50	36.0
No	89	64.0

Table 2: Spearman's rank correlation coefficients of dose volume parameters and acute esophagus toxicity (AET). * correlation is significant at the 0.05 level; **correlation is significant at the 0.01 level

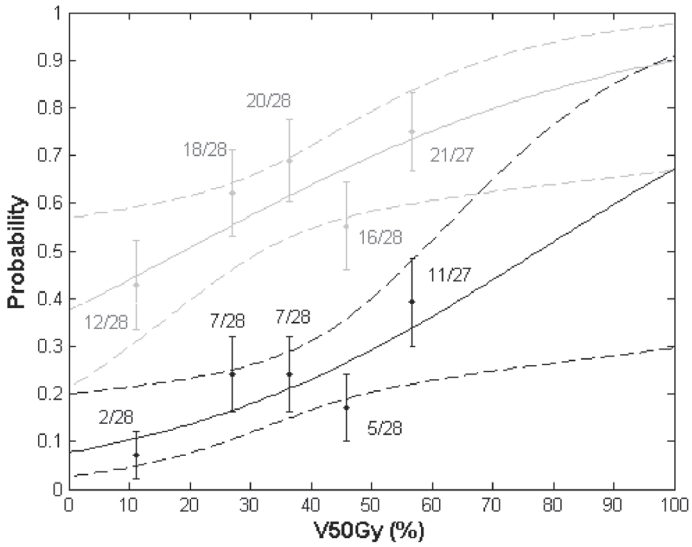
Variables	Correlation with AET	Correlation with V50
Dmax	0.237 **	0.536 **
Dmean	0.220 **	0.960 **
V5	0.104	0.665 **
V10	0.135	0.727 **
V15	0.149	0.764 **
V20	0.161	0.833 **
V25	0.174 *	0.876 **
V30	0.193 *	0.909 **
V35	0.222 **	0.944 **
V40	0.231 **	0.970 **
V45	0.250 **	0.991 **
V50	0.250 **	--
V55	0.265 **	0.989 **
V60	0.284 **	0.938 **
V65	0.300 **	0.856 **
V70	0.247 **	0.708 **

Table 3: Results of the backward stepwise regression analysis; Volume of the esophagus receiving ≥50 Gy (V50) to predict Acute Esophagus Toxicity grade 2 and 3

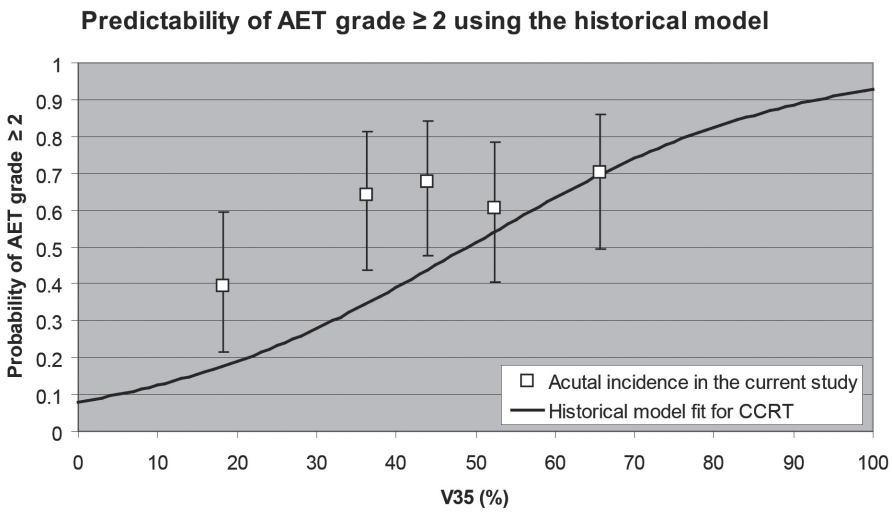
Acute Esophagus Toxicity	Variable	Coefficient	Standard deviation of the coefficient	p-value	Odds ratio
Grade 2	V50	0.027	0.011	0.012	1.027
	Constant	-0.515	0.405	0.204	0.598
Grade 3	V50	0.032	0.013	0.012	1.033
	Constant	-2.486	0.561	<0.001	0.083



▲**Figure 1:** Average esophageal dose-volume-histogram for the historical patients planned with conformal radiotherapy, and the current IMRT-dataset. The error bars denote the 95% standard error. Both groups were compared for each dose level using a 2-sided students T-test (*p<0.05, **p<0.01, ***p<0.001)



▲**Figure 2:** Probability of developing AET grade 2 (grey line) and grade 3 (black line) using the logistic model based on V50. The 95% confidence intervals are plotted in dash-dotted lines. The actual incidences, together with its 95% confidence intervals, are plotted in the vertical lines. CCRT = concurrent chemoradiotherapy.



▲**Figure 3:** Probability of developing grade ≥2 AET using the current clinical model based on V35 (solid line). The datapoints illustrate the actual incidence of AET based on the V35, and their 95% confidence intervals.

Discussion

To the best of our knowledge, this is the first analysis of dosimetric predictors of AET performed within a large patient group treated with IMRT and the same concurrent chemotherapy-regimen. Several studies have shown that treatment with CCRT gives an increased risk of AET [2,3,5-7], as was also confirmed in the current study. We showed that in the setting of CCRT, the incidence of AET was not significantly changed by the introduction of IMRT compared to 3DCRT. Our current clinical AET prediction model, using V35, resulted in inadequate prediction of AET grade ≥2 when treating with CCRT. With increasing incidence of grade 3 AET, prediction of grade 3 is deemed to be clinically more relevant, and we therefore propose to use the V50.

With the introduction of IMRT the volume of the esophagus receiving 5 to 40 Gy was significantly reduced, and simultaneously, the volume receiving 70 Gy was significantly increased (Figure 1). Using the historic prediction model based on V35 [2], one would expect that the incidence of grade ≥2 AET would have been reduced with IMRT, which was actually not the case. The inability of predicting AET using the V35 model in CCRT was indicated by the discrepancies between the actual incidence and the V35 prediction model (Figure 3). With use of CCRT, there were a substantial

proportion of patients with more severe grade 3 AET, independent of use of IMRT, which was not addressed in the old V35 model. An update of the prediction model was therefore needed.

For grade 3 AET, the V50 was shown to be the best predictor, and for grade 2 AET the V50 also showed to perform significantly better than the current V35 model. With no significant change in AET incidence compared to patients treated with 3DCRT, it is also logical to find the best predictor at a dosimetric level at which the volume of esophagus was not different between 3DCRT and IMRT (between V45 and V65, Figure 1).

Werner-Wasik et al. [7] described in their review that a higher dose, even on a small part of the esophagus, might be a risk factor for AET. They described several dosimetric parameters to be predictive in univariate analysis for grade 2 and 3 AET: V20 till V80. But most at risk for AET were esophagus volume doses receiving >40-50 Gy. This data is consistent with our analysis, were V15 till V70 and D_{mean} and D_{max} of the esophagus were all significantly correlated with AET.

The systematic review of Rose et al. [6] demonstrated that the $D_{mean,}$ V20, V30, V40, V45 and V50 were the most studied dosimetric predictors, showing high levels of association with AET. The dosimetric predictors of AET in Rose's review are consistent with the most significant predictor we found, the V50.

Caglar et.al. published an analysis based on 3DCRT and concurrent chemotherapy with 109 patients [4]. These patients were treated with or without induction chemotherapy followed by CCRT with different chemotherapy regimens. Radiotherapy dose varied between 50-68 Gy in 2 Gy fractions. V45 till V60 were indicated as most predictive dose-volume-parameters for AET. Besides the dose on the entire esophagus, Caglar et al. studied the region of the esophagus exposed to a high dose (esophagus infield). The V55 of the entire esophagus and esophagus infield was the most significant parameter to predict AET in multivariate analysis. They showed that when the D_{mean} of the esophagus infield was below 50 Gy, no grade 3 occured. In our analysis we did not specify between entire esophagus dose and esophagus infield, but the dose of 50 Gy is in agreement with our V50 for predicting grade 3 AET.

In the current study RT was given with 2.75 Gy fractions. Despite the increased fraction dose, the incidence of grade 3 AET was not higher compared to Caglar et al. [4] (25%), where conventional 2 Gy fractions were used. The radiotherapy dose of our study

was converted into NTD equivalent to fraction doses of 2 Gy with α/β=10, for which the derived results may also be applied to other fractionation schemes providing the same α/β is used. Uitterhoeve et. al. reported in a phase I/II EORTC trial that this fractionation-scheme was safe using 3DCRT and an EORTC phase III multicenter trial confirmed this[13,14]. In 2005 the NKI-AVL introduced IMRT for all lung cancer patients treated with radical intent and to our clinical experience the safety of this treatment is well established. Uyterlinde et. al. analyzed that our CCRT regimen with IMRT is well tolerated in cohort of 188 patients [15].

For the treatment of stage III NSCLC patients, a certain risk of grade 3 AET is deemed acceptable because the toxicity is often temporary and manageable. Late esophagus toxicity (LET) like a fistula or stricture of the esophagus may however cause life-threatening problems for the patient. For LET, proposed predictive parameters are Dmean and V50 [6], and V45 to V60 [4], but most studies analyzing LET were done in patient groups treated with heterogeneous radiotherapy and chemotherapy schedules. Belderbos et al. reported from the randomized trial comparing sequential (N=78) and concurrent (N=80) chemoradiation that a higher incidence of AET in the CCRT-arm did not result in a higher incidence of severe late toxicity (4 vs. 5 %). Follow-up of the patients included in the current study is ongoing to report LET in the future.

Limitations of the study

Limitations in general were the difficulties encountered with the scoring of AET in patients treated with CCRT. Although we scored prospectively, sometimes it is difficult to differentiate between AET and side effects of chemotherapy (e.g. anorexia).

The dose-volume-parameters were all based on the position of the esophagus during the midV-scan and were not corrected for movements of the esophagus during treatment. Motion analysis of the esophagus, and also the influence of length and circumference of the irradiated esophagus on AET is currently being investigated to further increase our knowledge on AET.

Our CCRT treatment consists of daily low dose Cisplatin but different chemotherapy-regimens are frequently used. Currently this radiotherapy scheme and full-dose concurrent chemotherapy is being tested in a randomized phase II trial (study identification-number NCT-01024829).

Conclusions

For NSCLC patients treated with CCRT and IMRT, the V50 was identified as most accurate predictor of grade ≥3 AET. We advise to introduce the V50 model in clinical practice in order to reduce the risk of AET, and have a better prediction of severe acute esophageal toxicity. There is no difference in the incidence of grade ≥2 AET between 3DCRT and IMRT in patients treated with CCRT.

References

1. Auperin A, Le Pechoux C, Rolland E et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181-2190.
2. Belderbos J, Heemsbergen W, Hoogeman M et al. Acute esophageal toxicity in non-small cell lung cancer patients after high dose conformal radiotherapy. Radiother Oncol 2005;75:157-164.
3. Bradley J, Deasy JO, Bentzen S et al. Dosimetric correlates for acute esophagitis in patients treated with radiotherapy for lung carcinoma. Int J Radiat Oncol Biol Phys 2004;58:1106-1113.
4. Caglar HB, Othus M, Allen AM. Esophagus in-field: a new predictor for esophagitis. Radiother Oncol 2010;97:48-53.
5. Dehing-Oberije C, De Ruysscher D, Petit S et al. Development, external validation and clinical usefulness of a practical prediction model for radiation-induced dysphagia in lung cancer patients. Radiother Oncol 2010;97:455-461.
6. Rose J, Rodrigues G, Yaremko B et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 2009;91:282-287.
7. Werner-Wasik M, Yorke E, Deasy J et al. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys 2010;76:S86-S93.
8. Chapet O, Thomas E, Kessler ML et al. Esophagus sparing with IMRT in lung tumor irradiation: an EUD-based optimization technique. Int J Radiat Oncol Biol Phys 2005;63:179-187.
9. Chapet O, Fraass BA, Ten Haken RK. Multiple fields may offer better esophagus sparing without increased probability of lung toxicity in optimized IMRT of lung tumors. Int J Radiat Oncol Biol Phys 2006;65:255-265.
10. Schwarz M, Alber M, Lebesque JV et al. Dose heterogeneity in the target volume and intensity-modulated radiotherapy to escalate the dose in the treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2005;62:561-570.
11. Wolthaus JW, Schneider C, Sonke JJ et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys 2006;65:1560-1571.
12. van Herk M. Errors and margins in radiotherapy. Semin Radiat Oncol 2004;14:52-64.
13. Belderbos J, Uitterhoeve L, van Zandwijk N et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). Eur J Cancer 2007;43:114-121.
14. Uitterhoeve AL, Belderbos JS, Koolen MG et al. Toxicity of high-dose radiotherapy combined with daily cisplatin in non-small cell lung cancer: results of the EORTC 08912 phase I/II study. European Organization for Research and Treatment of Cancer. Eur J Cancer 2000;36:592-600.
15. Uyterlinde W, van den Heuvel M, Belderbos J. Correlation of co-morbidity, patient characteristics and the occurrence of toxicity due to concurrent, sequential chemo radiotherapy or high dose radiotherapy alone, in patients with locally advanced non small cell lung cancer. Abstract P4-238, 07-2011. World Conference of Lung Cancer.

CHAPTER 7

THE USE OF REAL-WORLD EVIDENCE TO AUDIT NTCP - MODELS FOR ACUTE ESOPHAGEAL TOXICITY IN NON-SMALL CELL LUNG CANCER PATIENTS

M.H. Kwint, I. Walraven, M. Verheij, J-J Sonke, J.S.A. Belderbos, T.M. Janssen

Radiother Oncol. 2020;146:52-57. doi:10.1016/j.radonc.2020.02.006

Introduction

The aim of this work is to assess the validity of real world data (RWD) derived from an electronic toxicity registration (ETR). As a showcase, the NTCP-models of acute esophageal toxicity (AET) for concurrent chemoradiation (CCRT) for NSCLC patients were used to validate the ETR of AET before/after dose de-escalation to the mediastinal lymph nodes.

Material and Methods

One hundred and one patients received 24x2.75 Gy and 116 patients received de-escalated dose of 24x2.42 Gy to the mediastinal lymph nodes. The validity and completeness of the ETR was analyzed. The grade ≥2 AET probability was defined according the V50 Gy and V60 Gy NTCP-models from literature. Validity of the models was assessed by calibration and discrimination. Furthermore, sensitivity and specificity for different cut-off points were determined.

Results

The compliance of ETR was 73-80%, with sensitivity and specificity rates of 83% and 86% for grade ≥2 AET, respectively. Discrimination of both NTCP-models demonstrated a moderate accuracy (V50 model = AUC of 0.71; V60-model AUC= 0.69). Dose de-escalation did not influence the accuracy of the V50-model; AUC before: 0.69, and AUC after: 0.71. For the V60-model the model-accuracy decreased after dose de-escalation; before AUC= 0.72 and after AUC 0.62, respectively.

Conclusion

RWD is a useful method to audit NTCP models in clinical practice. The NTCP models to predict AET in NSCLC patients showed good predictive accuracy. For clinical practice, the V50 Gy seems to be most stable for dose de-escalation without compromising safety and efficacy.

Introduction

Randomized clinical trials (RCTs) provide the highest level of evidence to prove treatment efficacy and safety. When evidence from RCTs is lacking, clinical decision-making is typically supported by data from observational studies and clinical registries. Collectively, data obtained from sources outside RCTs are often referred to as 'real world data' (RWD), and the evidence derived from aggregation and analysis of such data as real world evidence (RWE) (1-5). RWE is often criticized due to its presumed lack of validity because of the broad patient heterogeneity and the vast amount of missing data compared to data derived from RCTs (1).

With the introduction of electronic medical records, a more systematic and accurate recording of treatment related toxicity was implemented in clinical practice (6, 7). Such a toxicity registration, when consistently used for all patients, provides a large amount of data, possibly useful for the evaluation of treatment quality since this data can easily be associated with patient characteristics and/or treatment parameters. Nonetheless, the completeness and validity of this 'big data' remains uncertain. Therefore, validation is needed to define the accuracy of such a registration to provide RWE (1, 8, 9).

For patients with locally advanced non-small cell lung cancer (NSCLC), the treatment of choice is concurrent chemoradiation (CCRT)(10-12). The addition of chemotherapy provokes a radiosensitizing effect leading to an improved local tumor control and overall survival, compared to radiotherapy only or sequential chemoradiation. But this comes at the cost of an increase of acute esophageal toxicity (AET)(13). Several studies have reported (14-20) on different dosimetric and clinical parameters to predict the risk of AET with the use of Intensity Modulated Radiotherapy (IMRT). We previously investigated the dose-effect relation between dose volume parameters and AET (16) and identified the V50 (volume of the esophagus receiving ≥ 50 Gy) as the most accurate predictor of AET. Palma et al. (17) performed an individual-patient-data meta-analysis and concluded that the V60 (volume of the esophagus receiving ≥60 Gy) was the most accurate predictor for AET.

The aim of this work is to assess the validity of a RWD toxicity registration and to show the feasibility of such an infrastructure to audit toxicity prediction models and dose constraints in daily clinical practice. Since June 2015 the dose to the irradiated mediastinal lymph nodes was de-escalated from 66 Gy to 58.08 Gy (60 Gy (EQD2))

in 24 fractions) for NSCLC patient treated with CCRT (21, 22). As a showcase, the electronic registration of AET was used to validate the applicability of this RWD for the NTCP models of AET for CCRT for NSCLC-patients, for 2 sequential cohorts.

Materials and Methods

Patient selection

A consecutive cohort of patients treated with CCRT for cytologically or histologically proven NSCLC in our institute between 2014 and 2016, were selected for this analysis. The clinical AET grades from the electronic toxicity registration as well as patient characteristics and dose-volume-parameters of the esophagus were available for all patients. Baseline characteristics are presented as mean (+standard deviation (SD)) or median (+ interquartile range) in case of a skewed distribution or proportions.

Treatment

The concurrent chemotherapy regimen consisted of daily low dose Cisplatin intravenous (6 mg/m²) 1-2h before irradiation. The patients treated between January 2014 until June 2015 were treated with IMRT of 66 Gy to the primary tumor and mediastinal lymph nodes in 24 fractions, once daily, 5 times per week. Since the 1st of June 2015 the dose on the irradiated mediastinal lymph nodes was de-escalated from 66Gy to 58.08 Gy (60 Gy BED) in 24 fractions (21, 22). Therefore, this dose de-escalation was used as a showcase to audit the quality of the NTCP-models before/after this treatment adaptation with the use of RWD.

Radiotherapy preparation

For all patients a 3D-midventilation-CT (MidV-CT) was selected out of a respiration correlated 4DCT, in which the moving tumor was closest to its time-averaged mean position (23). The gross tumor volume (GTV) and all pathological lymph nodes were delineated on the MidV-CT which was also registered with a recent fludeoxyglucose-positron-emission-tomography-(FDG-PET)-scan. The GTV was expanded to a planning target volume (PTV) using a personalized margin protocol based upon the tumor and lymph node movement during breathing. Critical organs were delineated according to a written protocol: heart, spinal cord, lungs and esophagus (from cricoid to gastro-esophageal-junction). The planning-constraints used for the organs at

risk were; esophagus: Dmax ≤66 Gy and V(50Gy) ≤50% ($EQD2_{10}$), mean lung-dose ≤20 Gy ($EQD2_3$), spinal cord ≤52 Gy ($EQD2_2$), total heart ≤40 Gy and ⅔ of the heart ≤50 Gy and ⅓ of the heart ≤66 Gy ($EQD2_3$). Equally spaced, 7-field IMRT-plans were calculated and optimized using 10 and/or 6 MV photons. Optimization was done using direct machine parameter optimization in Pinnacle version 9.0, (Philips, Best, The Netherlands). The prescription dose was specified at a representative point in the PTV. The dose inhomogeneity within the PTV was >90% and <115%.

Electronic toxicity registration method

From December 2012, a prospective, electronic toxicity (grade ≥2 toxicities (CTCAE v4.0)) registration was implemented within our department. Registration of toxicity is performed by the treating physician during each patient consultation. Simultaneously, a data management infrastructure was built to merge the toxicity data to patient characteristics and treatment parameters.

AET was scored using the Common Toxicity Criteria 4.0 from start of treatment, till 3 months after. Toxicity was scored at baseline and weekly during treatment, until 3 weeks after treatment by the treating physician. Thereafter the patients were followed with 3 monthly intervals or more frequently if indicated. The toxicity was scored in the electronic patient file (Chipsoft, Amsterdam, The Netherlands). The physician first indicated whether or not any toxicity grade ≥2 was present. In case no or grade 1 toxicity was present, 'no toxicity' was scored to distinguish between missing data and an explicit registration of 'no toxicity'. When there was grade ≥2 toxicity, the type and grade of toxicity was registered. The highest AET grade was used for this analysis. The data from the first year of the toxicity registration (December 2012 until December 2013) was not used for this study. This first year was used to illustrate the learning curve of the registration of the physicians. To assess the validity and completeness of the electronic registration, a sample test of N=77 (35%) was performed to check the accuracy of the registration. This was done separately by two individuals, by retrospectively reviewing the patients file and compare this to the electronic toxicity registration. For this sample test, a cross table was made and sensitivity and specificity rates were calculated.

Dosimetric analysis

The physical RT-dose was converted to Normalized Total Dose (NTD) for 2 Gy per fraction with an α/β-ratio of 10 Gy for AET. With the NTD corrected dose, esophageal dose-volume-histograms (DVH) were computed and dose-volume-parameters V50 and V60 were derived.

The grade ≥2 AET probability was calculated as (16, 17);

V50-model: $1/(1 + \exp-(-0.515 + 0.027 * \mathrm{V50}))$

V60-model: $1/(1 + \exp-(-0.701 + (0.029 * \mathrm{V60}))$

The grade ≥3 AET probability was calculated as (16, 17);

V50-model: $1/(1 + \exp-(-2.486 + (0.032 * \mathrm{V50})$

V60-model: $1/(1 + \exp-(-2.29 + (0.0286 * \mathrm{V60}))$

Validity of the model was assessed as the ability to predict the number of grade ≥2 and grade ≥3 AET events (calibration). A receiver operating characteristic curve (ROC-curve) was used to analyze the predictive ability of the V50 and V60 prediction models. The area under the curve (AUC) was calculated to distinguish between those who develop grade ≥2 AET. For clinical use, the ability to identify the true positive (sensitivity) patients is more important than the false negative patients (specificity). Therefore, the optimal cut-off point of the model (probability to predict AET) was based on the highest sensitivity.

The following sensitivity analyses for quality assurance were performed. A Mann Whitney test was used to compare the median V50 and V60 before and after 1st of June 2015 (Since 1st of June 2015 the dose on the irradiated mediastinal lymph nodes was de-escalated to 58.08 Gy in 24 fractions). Thereafter a ROC-curve was used to analyze the predictive ability between the 2 periods (before and after dose de-escalation) for grade ≥2 AET for both V50- and V60-models. The Delong-test was used to analyze the significance differences in AUCs (24, 25). All statistical analyses were performed using IBM SPSS (version 22).

Results

Two hundred and seventeen consecutive patients were included in this study (**Table 1**). Mean age was 62 years (SD 8.9 year). One hundred and one patients were treated before 1st of June 2015 when the prescription dose was 66 Gy in 24 fractions on the primary tumor and pathological lymph nodes and 116 patients were treated after dose de-escalation with a prescription dose of 66 Gy in 24 fractions on the primary tumor and 58.08 Gy in 24 fractions on the pathological lymph nodes. Ninety-five patients developed grade 2 AET (44%) and AET grade 3 was seen in 12 patients (6%) according to the electronic toxicity registration. No AET grade 4 and 5 were registered. Due to the low incidence of grade 3 AET (6%) and corresponding low power, further analyses on grade 3 AET were not possible. Therefore, validation of the V50- and V60 NTCP-models for prediction was only performed for grade ≥2 AET.

Validation of electronic toxicity registration

The period from December 2012 until December 2013 was considered a learning period for the physicians to get used to the toxicity registration in the electronic medical record. Compliance of toxicity registration in de the electronic medical record increased over this year from 48% to 60% of all appointments. After additional training, compliance increased further to an average of 73%, 80% and 80% for the years 2014, 2015 and 2016 respectively. This means that in 73% - 80% of the patients, the absence/presence of toxicities were registered.

The results of the sample test to assess the validity of the electronic toxicity registration are shown in **Table 2**. For this sample test, the sensitivity of the electronic toxicity registration for grade ≥2 AET (when the independent validation is the gold standard) was 83%, with a specificity of 86%.

Table 1: Patients and tumor characteristics. WHO = world health organization, NOS: not otherwise specified. TNM 7th edition was used for staging.

Patient and tumor characteristics	N (%)
Sex	
Male	118 (54%)
Female	99 (46%)
WHO performance status	
0	85 (39%)
1	123 (57%)
2	9 (4%)
Stage (ignoring M-status)	
1A	0 (0%)
1B	5 (2%)
2A	2 (1%)
2B	13 (6%)
3A	123 (57)
3B	74 (34%)
T-stage	
T0-Tx	12 (6%)
T1	29 (13%)
T2	46 (21%)
T3	56 (26%)
T4	74 (34%)
Nodal stage	
N0	40 (18%)
N1	18 (9%)
N2	122 (56%)
N3	37 (17%)
Pathology	
Adenocarcinoma	96 (44%)
Squamouscellcarcinoma	73 (34%)
Non-small-cell lung cancer NOS	48 (22%)

Table 2: Cross tabulation of the sample test of 77 patients. AET = Acute Esophagus Toxicity, ETR = Electronic Toxicity Registration.

AET	Grade 0-1 ETR	Grade 2 ETR	Grade 3 ETR	Total
Grade 0-1 observer	31	5	0	36
Grade 2 observer	5	25	0	30
Grade 3 observer	2	4	5	11
Total	38	34	5	77

Validation of V50- and V60-model

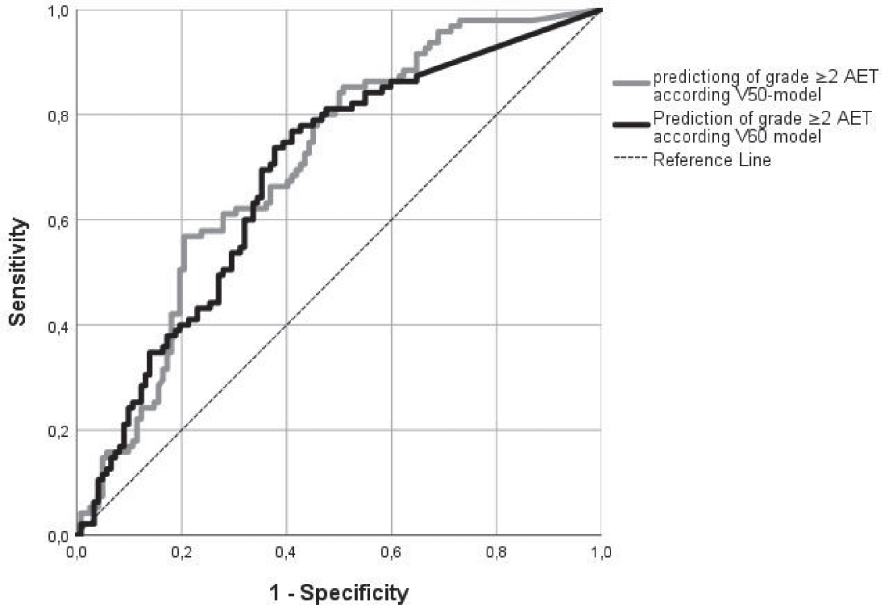
Median V50 was 22.9% (IQR 10.3% - 35.7%) and the median V60 was 5.1% (IQR 0.0% - 20.96%). Discrimination of both algorithms demonstrated a similar moderate accuracy with an area under the curve (AUC) of 0.706 (95%CI 0.637 to 0.775) for the V50 model and an AUC of 0.685 (95% CI 0.614 to 0.757) for the V60 model, respectively (**Figure 1**). Calibration showed that the V50-model slightly overestimated the risk of developing grade ≥2 AET in low-risk (predicted incidence <50%) patients while in high risk patients (predicted incidence >50%) the predicted incidence was in accordance with the observed incidence of grade ≥2 AET. The V60-model overestimated the risk of developing grade ≥2 AET in low-risk patients and underestimated the risk of developing grade ≥2 AET in high-risk patients (**Figure 2&3**).

In both models, the sensitivity was higher for lower cut-off points and the specificity was higher for higher cut-off points. For the V50-model, a cut-off point of more than 40% probability of developing grade AET resulted in the most favorable sensitivity of 95.8% for grade ≥2 with specificity scores of 30.1%. For the V60-model, this cut-off point resulted in a sensitivity of 68.3% for grade ≥2 with specificity scores of 58.8%.

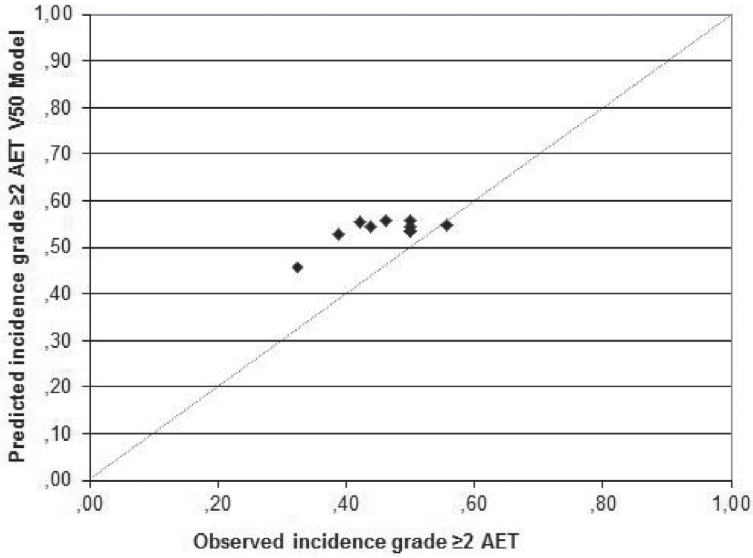
Validation V50- and V60-model before and after dose de-escalation

The patient cohort was split into a population before and after dose de-escalation. The median V60 decreased significantly (p=0.001) after the dose de-escalation on the mediastinal lymph nodes from 12.7% (IQR 25.3%) to 1.3% (IQR 17.1%). The median V50 decreased as well (from 26.9% (IQR 23.5%) to 21.7% (IQR 24.6%)) but this was not significant (p=0.120).

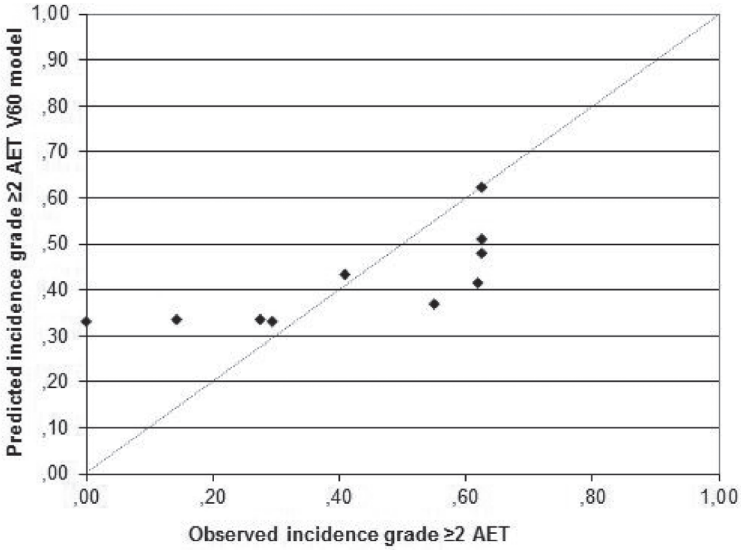
The incidence of grade ≥2 and grade ≥3 AET decreased after de-escalation of the mediastinal lymph nodes from 50.5% to 37.9% (p=0.032) and 7.9% to 3.4% (p=0.076) respectively. We compared the accuracy of the V50- and V60-model for grade ≥2 AET between the 2 time periods (**Figure 4**). For the V50-model, an almost similar model fit was found with an AUC of 0.690 (95%CI 0.585-0.795) before dose de-escalation and 0.707 (95%CI 0.609 – 0.804) after. For the V60-model, the model fit decreased after dose de-escalation; AUC= 0.722 (95%CI 0.621 – 0.823) compared to 0.624 (95%CI 0.518 – 0.729), respectively (**Figure 2**). The Delong-test (24, 25) showed no significant differences between AUC of both models (p= 0.41 (V50-model) and p=0.09 (V60-model)).



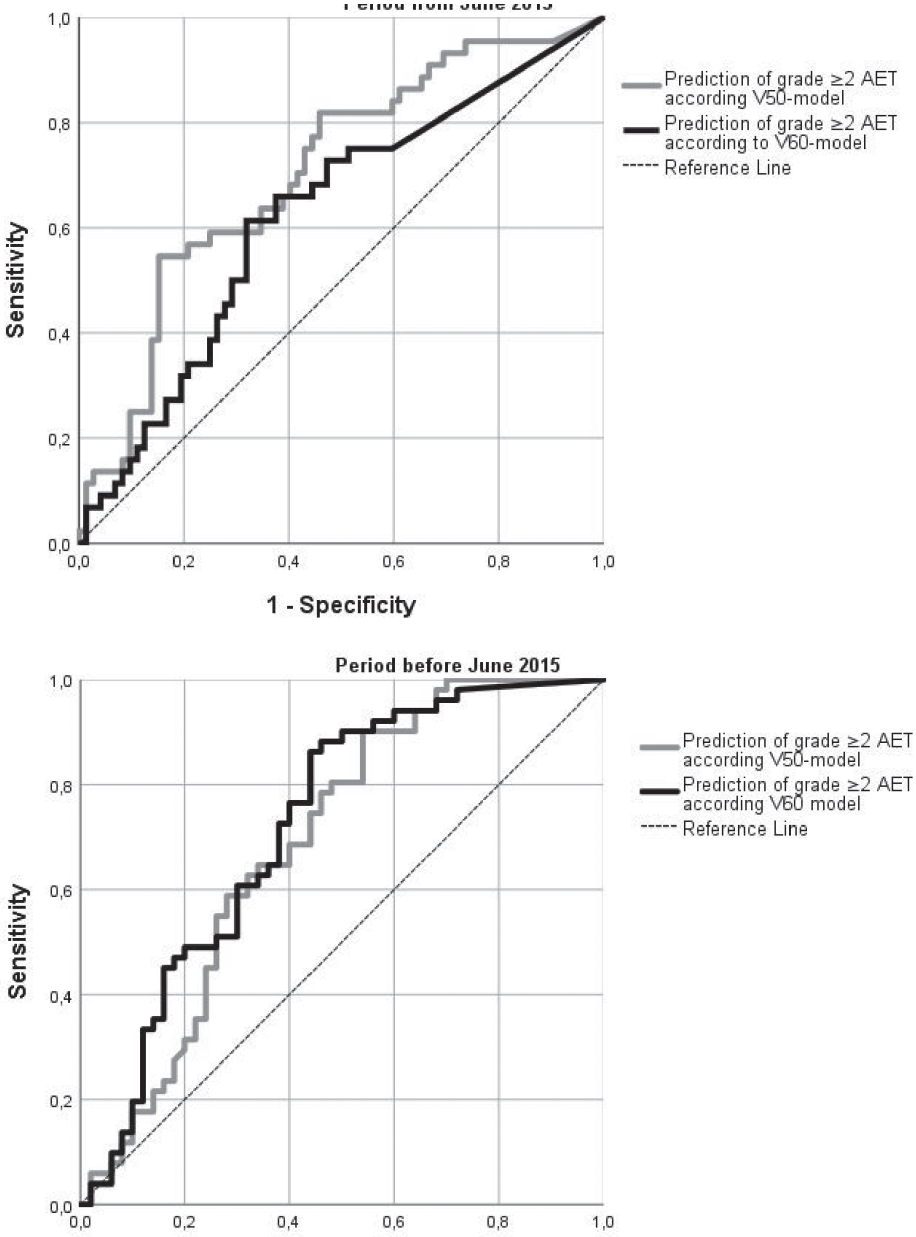
▲**Figure 1:** ROC-curve of the V50 and V60 predictive models for acute esophagus toxicity grade ≥ 2.



▲**Figure 2:** Calibration plot of the observed incidence of grade ≥2 Acute Esophagus Toxicity (AET) versus the predicted incidence of grade ≥2 Acute Esophagus Toxicity for the V50 model.



▲**Figure 3:** Calibration plot of the observed incidence of grade ≥2 Acute Esophagus Toxicity (AET) versus the predicted incidence of grade ≥2 Acute Esophagus Toxicity for the V60 model.



▲**Figure 4:** ROC-curve of the V50 and V60 predictive AET models grade ≥2 for time periods before and from June 2015. (AET = Acute Esophagus Toxicity)

Discussion

This study illustrates that real world data (RWD), gathered from an electronic toxicity registration (ETR), is a useful method to audit NTCP-models. The showcase, used in this study, exemplifies that with the use of RWD, the accuracy of the AET prediction models were influenced by the dose de-escalation of the involved mediastinal lymph nodes for CCRT in NSCLC patients.

The use of digital toxicity registration in electronic medical records is becoming more common practice in many radiotherapy departments. With this approach, a more systematic and accurate recording of radiotherapy toxicity can be achieved (6, 7). With regular adaptations in radiotherapy treatment schedules, techniques or prescription doses it is necessary to assure and maintain treatment quality. The use of RWD simplifies and accelerates quality assurance and provides tools to validate NTCP models in current clinical practice. Of course, (randomized) clinical trials remain a powerful method for developing scientific evidence. Nonetheless, RWD can be used to complement or audit the knowledge gained from traditional clinical trials, and provides additional insights on generalizability of RCT outcomes to the real world population. But to interpret this RWD right, it is important to use adequate analytic approaches to analyze the data and to use the right data-sources to collect the data (1).

AET is a common and severe toxicity of CCRT which has a negative influence on quality of life. Therefore, it is important to predict AET to mitigate the risk and to improve the therapeutic ratio of CCRT. The literature available on prediction models for AET and IMRT concluded that the high dose volumes are more important than the low dose volumes (14-19). In our previous work, the V50 was identified as an accurate predictor of AET for IMRT (16). In our hospital, the V50 is currently used as predictor for AET and dose constraint for the treatment planning. The meta-analysis of Palma et al. (17) analyzed the data of 1082 patients and concluded that the V60 has the best predictive ability (3D-CRT and IMRT). In the guidelines for radical radiotherapy from the Advisory Committee on Radiation Oncology Practice (ACROP) of the European Society for Radiotherapy and Oncology (ESTRO), the V60 is advised as dosimetric parameter to predict AET (26). We therefore decided to audit both parameters. AUCs for both the V50-model and the V60-model showed a moderate accuracy. Palma et al. found a lower AUC of 0.583 for the V60-model for grade ≥2 AET compared to ours

(AUC = 0.685 respectively). Our data is only IMRT based, and the dose heterogeneity due to IMRT, makes the higher dose parameters a better predictor for AET (14-18) compared to IMRT and 3D-CRT data in the study of Palma et al.(17).

A significantly lower median V60 dose on the esophagus was found after the dose de-escalation on the pathological lymph nodes. This resulted also in a significantly lower incidence of AET grade ≥2. With the de-escalation of the prescription dose from 66 Gy to 58.08 Gy (60 Gy EQD2) in 24 fractions on the mediastinum (i.e., the esophagus area), we found that the model accuracy of the V50-model was equivalent but the model accuracy of the V60-model was declined (AUC= 0.722 compared to an AUC = 0.624), p=0.09). Qualitatively this can be understood by the realization that the dose parameter that predicts AET is basically the volume of the esophagus receiving a high dose and less related to the specific value of V60. With a dose prescription of 58 Gy, it is expected that the V60 correlates less well with this volume, leading to a decline in model performance. Therefore, the V50-model is more robust in our clinical practice. Since radiation techniques and prescriptions doses differ in time the use of EUD models to predict AET, might be less amendable for these changes, but are not widely used in clinical practice (18).

We performed a sample test (N=77) to validate the quality of the electronic toxicity registration. This test showed a sensitivity of 83% and a specificity of 86% for the electronic registration of grade ≥2 AET. The compliance of the toxicity registration was 73-80%. This means that there is missing data. A limitation of this study is this missing data and that the sensitivity and specificity of <100% could have influenced the model accuracy. Comparison with the incidence of AET in the study of Van diessen et. al (22), similar incidences are found. This substantiate that RWD for ETR is reliable.

To conclude, the use of real world data provides a useful method for quality assurance and for validation of NTCP-models in clinical practice. Both V50 and V60 NTCP-models showed moderate accuracy to predict acute oesophageal toxicity in NSCLC patients. For clinical practice, the V50Gy seems to be the most stable to the dose de-escalation and sensitive without compromising safety and efficacy.

Reference

1. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016;375(23):2293-7.
2. Network for Exellence in Health Innovation. Real world evidence: a new era for health care innovation September 2015 [Available from: http://www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf.
3. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer. 2014;110(3):551-5.
4. Salathe M, Bengtsson L, Bodnar TJ, Brewer DD, Brownstein JS, Buckee C, et al. Digital epidemiology. PLoS Comput Biol. 2012;8(7):e1002616.
5. Califf RM. Pragmatic clinical trials: Emerging challenges and new roles for statisticians. Clin Trials. 2016;13(5):471-7.
6. Akbarov A, Williams R, Brown B, Mamas M, Peek N, Buchan I, et al. A Two-stage Dynamic Model to Enable Updating of Clinical Risk Prediction from Longitudinal Health Record Data: Illustrated with Kidney Function. Stud Health Technol Inform. 2015;216:696-700.
7. Tamblyn R, Girard N, Dixon WG, Haas J, Bates DW, Sheppard T, et al. Pharmacosurveillance without borders: electronic health records in different countries can be used to address important methodological issues in estimating the risk of adverse events. J Clin Epidemiol. 2016;77:101-11.
8. Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S3-9.
9. Jackson A, Marks LB, Bentzen SM, Eisbruch A, Yorke ED, Ten Haken RK, et al. The lessons of QUANTEC: recommendations for reporting and gathering data on dose-volume dependencies of treatment outcome. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S155-60.
10. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-90.
11. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010(6):CD002140.
12. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21.
13. Choy H, LaPorte K, Knill-Selby E, Mohr P, Shyr Y. Esophagitis in combined modality therapy for locally advanced non-small cell lung cancer. Semin Radiat Oncol. 1999;9(2 Suppl 1):90-6.
14. Wijsman R, Dankers F, Troost EG, Hoffmann AL, van der Heijden EH, de Geus-Oei LF, et al. Multivariable normal-tissue complication modeling of acute esophageal toxicity in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy. Radiother Oncol. 2015;117(1):49-54.
15. Gomez DR, Tucker SL, Martel MK, Mohan R, Balter PA, Lopez Guerra JL, et al. Predictors of high-grade esophagitis after definitive three-dimensional conformal therapy, intensity-modulated radiation therapy, or proton beam therapy for non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2012;84(4):1010-6.

16. Kwint M, Uyterlinde W, Nijkamp J, Chen C, de Bois J, Sonke JJ, et al. Acute esophagus toxicity in lung cancer patients after intensity modulated radiation therapy and concurrent chemotherapy. Int J Radiat Oncol Biol Phys. 2012;84(2):e223-8.
17. Palma DA, Senan S, Oberije C, Belderbos J, de Dios NR, Bradley JD, et al. Predicting esophagitis after chemoradiation therapy for non-small cell lung cancer: an individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87(4):690-6.
18. Nijkamp J, Rossi M, Lebesque J, Belderbos J, van den Heuvel M, Kwint M, et al. Relating acute esophagitis to radiotherapy dose using FDG-PET in concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer. Radiother Oncol. 2013;106(1):118-23.
19. Chen C, Uyterlinde W, Sonke JJ, de Bois J, van den Heuvel M, Belderbos J. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. Radiother Oncol. 2013;108(2):337-41.
20. Rose J, Rodrigues G, Yaremko B, Lock M, D'Souza D. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol. 2009;91(3):282-7.
21. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.
22. van Diessen JNA, Kwint M, Sonke JJ, Walraven I, Stam B, de Langen AJ, et al. Safety and efficacy of reduced dose and margins to involved lymph node metastases in locally advanced NSCLC patients. Radiother Oncol. 2019.
23. Wolthaus JW, Schneider C, Sonke JJ, van Herk M, Belderbos JS, Rossi MM, et al. Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. Int J Radiat Oncol Biol Phys. 2006;65(5):1560-71.
24. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982;143(1):29-36.
25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837-45.
26. Nestle U, De Ruysscher D, Ricardi U, Geets X, Belderbos J, Pottgen C, et al. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. Radiother Oncol. 2018;127(1):1-5.
27. Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008;56(1):45-50.

CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

General discussion and future perspectives

Main findings and summary of results

The aim of this thesis was to explore strategies to optimize radiotherapy for locally advanced non-small cell lung cancer patients (LA-NSCLC). In the first part we investigated if a modified dose prescription resulted in improved treatment outcomes for LA-NSCLC (**Chapter 2**) and for oligo-metastasized treatment (**Chapter 3**). In the second part, optimization of the radiotherapy with the use of image guided radiotherapy (IGRT) was studied **(Chapter 4 & 5)**. In the last part, normal tissue complication probability (NTCP) models for acute esophagus toxicity (AET) in radically treated LA-NSCLC patients were investigated **(Chapter 6 & 7)**. In this final chapter, the findings of this thesis are discussed and recommendations for future research are presented.

Part I Dose prescription and patient selection

Optimization of radiotherapy by dose alteration

The standard treatment of LA-NSCLC is concurrent chemoradiotherapy (CCRT) (1). In patients without progression, adjuvant immunotherapy is administered afterwards and part of the current standard of care (2, 3). In the past, different treatment strategies have been tested to improve local control and overall survival (OS) for LA-NSCLC patients. One of these strategies is dose escalation. Recently, an unexpected poor OS was associated with dose escalation in two randomized trials (RTOG 0617 and the trial of Hallqvist et.al.) (4, 5). In those studies, dose-escalation with prolonged overall treatment time was given in the experimental arm (74 and 84 Gy versus 60 Gy in 2 Gy). Other factors associated with poor OS in these studies were, tumor location, institution accrual volume, esophagitis, PTV and heart dose (V5). It has been suggested that the extended overall treatment time contributed to the poor OS in the experimental arm. Therefore, new interest is growing in dose-escalation using hypofractionation. In the Netherlands Cancer Institute, patients are treated with a mildly hypofractionated radiotherapy schedule of 24x2.75 Gy, combined with daily low dose Cisplatin, which is different from the international standard of 30x2 Gy and has been shown to have favorable outcomes compared to dose-escalation with extended treatment time (6-8).

The incidence of regional failures (lymph node metastases) after radiotherapy for LA-NSCLC is generally lower than local failures (primary tumor), around 10% versus 30% after 2 years (9-11). Tumor volume is a significant factor for predicting these regional and local failures (9). Since involved mediastinal lymph nodes have a smaller volume, compared to the primary tumor in the majority of patients, we hypothesized that the dose needed to control lymph node metastases might be lower than the dose needed to control the primary tumor. A consequence of a lower dose to the mediastinum might also induce an efficient reduction of the pulmonary, esophageal and cardiac toxicity rates.

In **Chapter 2**, an observational study of 308 locally advanced non-small cell lung cancer patients, compared 2 sequential cohorts, treated with a different radiation dose to involved mediastinal lymph nodes with or without concurrent or sequential chemotherapy. This study demonstrated that a differentiated dose prescription to the primary tumor (24x2.75 Gy) and the involved mediastinal lymph nodes (24x2.42 Gy), as well as a margin reduction of the primary tumor and lymph nodes, led to decreased radiotherapy induced pulmonary and esophageal toxicities and improved OS compared to the reference cohort (24x2.75 Gy to the primary tumor and lymph nodes). This study demonstrated that hypofractionated radiotherapy with a differentiated dose is a safe strategy with low toxicity risk and good OS (12). Recently, it was reported that the risk of heart disease in breast cancer patients, increased significantly within 5 years after treatment (13). Since the results of the RTOG 0617 (4), more awareness has arisen that heart dose is associated with a reduced OS in lung cancer patients. Lately, in a systematic review of Zhang et al. (14) it was concluded that 20 different cardiac dose-volume parameters were significantly associated with OS in NSCLC patients. However, no consistency in these heart dose volume parameters was found. We demonstrated that dose de-escalation to the mediastinal lymph nodes and PTV-margin reduction resulted in lower heart, esophageal and lung dose, reduced toxicities, and improved OS. To further enhance treatment outcomes, improvements of radiation dose distributions and/or escalation to the primary tumor are crucial. A potential approach which facilitates dose escalation to the primary tumor, while not exceeding the dose constraints of the organs at risk (OAR), is isotoxic treatment planning. This is a personalized treatment planning method in which the maximum achievable biologically effective dose (BED) to the tumor is given, until predefined dose constraints on the OAR are reached.

Several trials investigated dose escalation using such isotoxic planning strategy without extending the overall treatment time (15-19). An overview is given in Table 1. The reported acute and late toxicity rates of these trials are classified 'acceptable'. Altogether, these studies indicate that dose escalation with reduced overall treatment time by increasing the dose per fraction or twice daily irradiation, is a promising method.

Several (randomized) trials are ongoing in which isotoxic hypofractionated dose escalation with the use of an FDG-PET scan are investigated (16, 20-24). The results regarding treatment outcomes are pending. The phase II PET boost trial (NCT01024829) (21) toxicity outcomes were recently reported (22). In this international trial, LA-NSCLC patients were randomized between dose escalation to the entire primary tumor (arm A) or to the high FDG-uptake region inside the primary tumor (>50% SUVmax, arm B), whilst giving 66 Gy in 24 fractions to the involved lymph nodes. Grade≥3 toxicity were reported in 41% (acute) and 25% (late) of the patients. In 9 patients (8%) fatal pulmonary hemorrhages and esophageal fistulas were observed (22). This is a higher incidence compared to our cohort results (acute & late toxicity combined grade≥3 was 29% and 10% for the reference- and reduction cohort respectively). In the PET boost trial, the same dose as our reference cohort (24x2.75 Gy) was given to the involved lymph nodes, however in patients selected with large primary tumors (> 4 cm). Combining these findings we can conclude that a differentiated dose prescription to the involved lymph nodes combined with dose escalation to the primary tumor with restricted overall treatment time, is a promising option for further testing.

To summarize, many recent studies revealed that the paradigm 'the higher the dose, the better the outcome' is not always true. Caution is required in dose escalation trials especially when dose-escalation is combined with a prolonged overall treatment time. Currently, new strategies for dose escalation are investigated, such as personalized isotoxic planning. These promising strategies will hopefully lead to further improved local control without compromising the dose to organs at risk.

Table 1: Overview of studies with dose escalation using isotoxic planning strategy without extending the overall treatment time. All dose values are expressed in Gy, AE acute esophagitis, AT acute toxicity, CCRT concurrent chemoradiation, D/Fx dose/fractions, Fx fractions, OTT overall treatment time, LRC local regional control, LT late toxicity, MLD mean lung dose, N number, NR not reported, OS overall survival, RILT radiation induced lung toxicity, RT radiotherapy, seq CRT sequential chemoradiation, TD total dose, Y year

Author year (ref)	Study type	Dose Escalation Method	Dose limiting parameters	Stage	N	TD (Gy)	Fx	D/Fx	OTT	Primairy end-point	Outcome (%)	Toxicity
Van Baardwijk2010 (19)	Prospective single arm	Isotoxic, Planning-CT + PET-CT	MLD max 19Gy, Spinal Cord Dmax 54Gy, Great Vessels or Bronchi Dmax 70.2 Gy, Brachial Plexus Dmax 66Gy	I & II inoperable and III, Seq CRT	166	50.4-79.2	28-44	1.8 (2 daily, 8h interval)	25 +/- 5.8 days	OS	1y OS = 68.7 2y OS= 45	Both AT (grade 3, 21.1%; grade 4, 2.4%) and LT (grade 3, 4.2%; grade 4, 1.8%) were acceptable.
Van Baardwijk 2012 (18)	Phase II	Isotoxic, Planning-CT + PET-CT	MLD max 19Gy, Spinal Cord Dmax 54Gy, Brachial Plexus Dmax 66Gy, central structures 74Gy	Stage III (Stage II n=1) CCRT	137	51-69	33-42	1.5-2.0 1.5 Gy fractions daily up to 45 Gy 8-h interval, followed by 1 daily fractions of 2 Gy	35 +/- 5.7 days	OS	2y OS=52.4	≥grade 3 AT 35.8%, of which AE in 25.5%. ≥3 grade LT 7.3%

Author year (ref)	Study type	Dose Escalation Method	Dose limiting parameters	Stage	N	TD (Gy)	Fx	D/Fx	OTT	Primairy end-point	Outcome (%)	Toxicity
Cannon 2013 (15)	Phase I Prospective single arm	Stratified risk Planning-CT +/- PET-CT	A Bayesian dose-escalation scheme incorporating predicted risk for pneumonitis, were subsequent patient were grouped in risk bins	All stages eligible Stage I/II =9%, Stage III = 71% Stage IV = 13%, Recurrent =8% RT and seq CRT	75	57.0-85.5	25	2.28- 3.42	5 weeks (33 days)	Maximum tolerated dose	2y LRC= 62 3y OS= 29	No grade 3 AT and LT, Grade 4 and 5 LT in 8%. The maximum tolerated dose was identified at 63.25 Gy /25 Fx
Kong 2017 (16)	Phase II, Prospective single arm	Isotoxic Planning-CT + Mid treatment FDG-PET	RILT grade 2	Inoperable/ irresec-table NSCLC stage I-III (90% stage III) CCRT (93%) and RT	42	63-86	30	2.1 – 2.8	6 weeks (40 days)	OS, LRC	2y LRC= 82 2y OS= 52 5y OS=30	Grade 3: esophagitis 12% , RILT 7% and cardiac toxicity 2%
Landau 2016 (17)	Phase I/II	Isotoxic Planning-CT	Split into 2 Group1: an escalating esophageal dose constraint Group2: Lung and other normal tissue dose constraints	Stage II & III CCRT	82	63-73	30	2.1 – 2.4	6 weeks (40 days)	Toxicity	1y OS=88 2y OS= 68	6% grade 3 AE, 4% grade 3 pneumonitis. 1 grade 5 esophageal perforation. 68Gy was declared esophageal maximum tolerated dose.

Patient selection for oligometastatic disease

Patients with stage IV NSCLC are considered incurable and are mainly treated with a palliative intent (25). However, when a patient presents with a limited number of metastases (oligometastatic disease), a more radical treatment regime instead of palliative treatment may be beneficial with respect to PFS and/or OS (26-29). **Chapter 3** describes the results of a retrospective cohort study of stage IV NSCLC patients (N=91) with ≤5 synchronous oligometastatic disease with a good performance status, who were treated with a radical treatment at the NKI (either with surgery or radiotherapy after systemic treatment). Favorable long-term PFS and OS (14 and 32 months, respectively) was found in this selected group of patients, compared to stage IV NSCLC patients who were treated with palliative chemotherapy only (1-year OS of 29% and a median OS of 6 months) (25).

Ideally, the benefits of a radical treatment for oligometastatic NSCLC are investigated within randomized phase III trials. Several randomized phase II trials showed improved treatment outcomes for an additional local consolidative treatment of the oligometastases compared to systemic treatment only as the standard of care (27-31). Two of these randomized studies were prematurely closed after interim analysis, due to a significant PFS benefit in the local consolidative therapy arm (27, 31). To learn more about the outcome of a radical local treatment for oligometastatic disease and the different states of oligometastatic disease, it is crucial that internationally, the same definitions are used. ESTRO and EORTC recently published a consensus report on the different states of oligometastatic disease (29). They distinguish 9 different states of oligometastatic disease as shown in Figure 1 (29). Consequently, the committee set up the OligoCare prospective multi-cohort trial with the aim to assess the prognostic value of the defined oligo states and the acceptance and compliance of these states within clinical practice (NCT03818503) (32). Besides uniform definitions of the different states of oligometastatic disease, another important knowledge gap is the number of metastases present to be considered for oligometastatic state. Currently, a maximum of 3-5 metastases is most often called oligometastatic disease (29, 33, 34). In our study, most patients had 1 metastasis (85%), with a maximum of 4 metastases. The SABR-COMET study (28) was a randomized phase II study in which 99 patients with a maximum of 5 synchronous metastases were randomized between either palliative standard of care or standard of care + SABR to all metastatic lesions. In this study, SABR was associated with improved OS compared to palliative care (me-

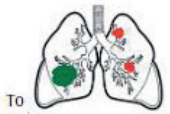
▶Figure 1: Illustration of the oligometastatic disease classification system
(A) De-novo oligometastatic disease. (B) Repeat oligometastatic disease. (C) Induced oligometastatic disease. In repeat and induced oligometastatic disease the primary tumor is assumed to be controlled by ongoing or previous treatment. Oligometastases are confirmed by imaging or biopsy to exclude simultaneous or secondary primary tumors. T0=at this current point of time. T-x=any previous point in time. *(Figure from Guckenberger et al. (29) published with copyright permission of The Lancet Oncology)*

dian OS: 41 months versus 28 months). However, only 18% of the included patients had NSCLC. Therefore, the impressive OS might be an overestimation for NSCLC patients, due to the overall better prognosis of prostate, colorectal and breast cancer patients compared to NSCLC. The outcome of the SABR-COMET study prompted the initiation of the randomized phase III study SABR-COMET-10 (NCT03721341) (35). This study is at the moment enrolling patients to assess the impact of SABR in patients with 4-10 metastatic lesions. Randomization is stratified by two factors: histology (Group 1: prostate, breast, or renal; Group 2: all others), and type of pre-specified systemic therapy (Group 1: immunotherapy/targeted; Group 2: cytotoxic; Group 3: observation). Hopefully these results will contribute to answer the clinical relevant question if patients with ≥4 metastatic lesions are indicated and safe for ablative therapies (35).

To conclude, consensus on the definition of oligometastatic disease is growing, but further research is necessary to investigate the association between the number of metastases, treatment options and overall survival in oligometastatic stage IV NSCLC patients.

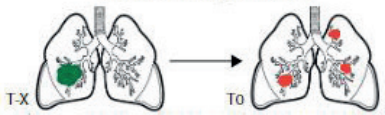
A De-novo oligometastatic disease

Synchronous oligometastatic disease



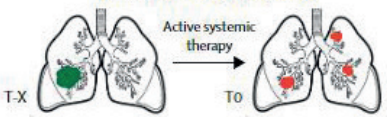
- T0: first time diagnosis of primary cancer (green) and oligometastases (red) within 6 months

Metachronous oligorecurrence



- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Systemic therapy-free interval
- T0: First time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

Metachronous oligoprogression



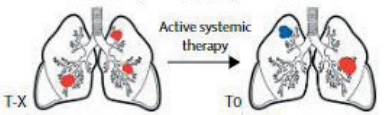
- T-X: diagnosis and treatment of primary cancer (green) in a non-metastatic state
- Under treatment with active systemic therapy
- T0: first time diagnosis of new oligometastases (red) >6 months after diagnosis of cancer

B Repeat oligometastatic disease

Repeat oligorecurrence

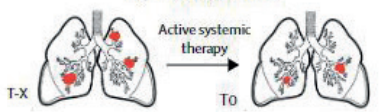
- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

Repeat oligoprogression



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases

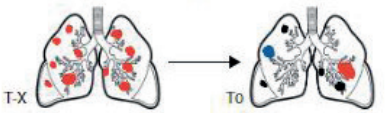
Repeat oligopersistence



- T-X: diagnosis of oligometastases followed by local treatment or systemic treatment or both
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive (red) oligometastases

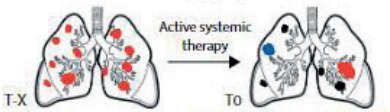
C Induced oligometastatic disease

Induced oligorecurrence



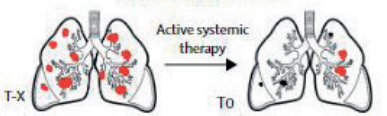
- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Systemic therapy-free interval
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligoprogression



- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of new (blue) and growing or regrowing (red) oligometastases, possible residual non-progressive metastases (black)

Induced oligopersistence



- T-X: diagnosis of polymetastatic metastatic disease followed by systemic treatment with or without local treatment
- Under treatment with active systemic therapy
- T0: diagnosis of persistent non-progressive oligometastases (red), where response is worse compared with other residual metastases (black)

Part II Image Guided Radiotherapy

Image guided radiotherapy and adaptive radiotherapy

Nowadays, image guided radiotherapy (IGRT) using CBCT for position verification and dosimetric quality assurance, is widely adopted in radiotherapy departments around the world (36). Repeated CBCT's made us aware of intra thoracic anatomical changes (ITAC) during the treatment course of lung cancer patients. In the Netherlands, CBCT's are typically analyzed by radiation therapy technologists (RTTs); the radiation oncologist is informed only when a change is observed. It is important that the RTT knows how to act on these detected ITACs. Therefore, a practical decision support system: "the traffic-light protocol", was developed in our institute to guide the RTT. **Chapter 4** describes the quantity of ITACs during the course of a radical radiotherapy treatment for LA-NSCLC patients. The traffic-light protocol has three urgency levels: red (considerable impact on dose distribution), orange (moderate impact on dose distribution) and green (negligible impact on dose distribution). The traffic-light protocol was retrospectively applied to all CBCT-scans of 177 patients. In the majority of the patients (72%) ITAC's were observed and 8% of the patients required a new planning CT-scan and an adapted treatment plan to account for anatomical changes. This study illustrated that ITACs indeed frequently occur and that it is important to have a practical decision support system in daily clinical practice to adequately react to these ITACs. Several studies reported on the dosimetric consequences of ITACs during treatment (37-39). A strategy to adjust for these ITACs is adaptive radiotherapy by performing a re-planning (40). Adaptive radiotherapy has the unique ability to prevent under dosing of the primary tumor or increased dose to the OARs when e.g. a tumor baseline shift or atelectasis occurs. Another advantage of adaptive radiotherapy is the possibility to reduce the dose to the OAR while maintaining the dose to the primary tumor after tumor regression is seen on a CBCT. This adaptive strategy raised the concern of local failure due to under dosing of microscopic disease in the new treatment plan. The LARTIA study (41) investigated the failure pattern of LA-NSCLC patients with an adaptive approach. A re-planning was performed in 50 out of 217 patients (23%). The decision of re-planning was based on regression seen on weekly CT-scans during treatment, visualized by 2 radiation oncologist, without a predetermined classification criteria. A local failure rate of 30% was reported (median follow-up of 25.8 months) in this trial which is comparable to the 25%-40% local failure rate in published literature (4, 9, 42, 43). Local failures were in-field (20%), marginal (6%), and

out-of-field (4%), respectively. The low incidence (6%) of marginal failures in this trial, supports an adaptive radiotherapy strategy to adjust for primary tumor regression. In **chapter 5** tumor volume regression during CCRT was investigated. In more than a third (35%) of the patients objective tumor regression during treatment was observed on CBCT. Three distinct subgroups of tumor volume change trajectories seen on a CBCT during CCRT for LA-NSCLC patients were identified in this study. Previously published studies indicated that tumor volume changes during treatment might be predictive for treatment outcomes (44-46). Surprisingly, no association between these subgroups and treatment outcome was found, whereas baseline volume of the primary tumor was significantly associated with OS. Our results were confirmed by the recent study of Amugongo et al. (47). Similarly to our study, 3 distinct subgroups of tumor volume change trajectories seen on CBCT were reported, but no significant association between these subgroups and OS was found. These findings demonstrate that tumor regression during treatment frequently occurs, and this has led to a new initiative in our institute, to analyze an adaptive radiotherapy re-planning approach based on tumor regression seen on the CBCT compared to non-adaptive radiotherapy for LA-NSCLC. This will be subject of future research in lung cancer patients irradiated with radical intent.

Part III Acute esophagus toxicity

NTCP-modelling of acute esophagus toxicity

As previously mentioned, for patients with LA-NSCLC, the treatment of choice is CCRT (1, 48, 49). The addition of chemotherapy provokes a radiosensitizing effect leading to improved local control and OS, compared to radiotherapy only or sequential chemoradiation. However, this comes at the cost of an increase of acute esophageal toxicity (AET) (50). In **chapter 6**, the V50 (volume of the esophagus receiving ≥50 Gy) was identified as an accurate predictor of AET with IMRT for NSCLC patients treated with CCRT. Nowadays, IMRT and Volumetric Modulated Arc Radiotherapy (VMAT) are commonly used techniques. These techniques have the ability to modulate the beam intensity during dose delivery, which leads to an increased dose conformality compared to 3DCRT (51, 52). In a retrospective study (N=188), a higher incidence of AET grade ≥2 was reported with VMAT compared to IMRT (51). This study also reported a not statistically significant higher rate of late pulmonary toxicity in VMAT patients. Since VMAT and IMRT have a different dose delivery and distribution, it is important

to verify and adjust the current 3DCRT-based NTCP-models for these new treatment techniques. A method to validate current NTCP-models is the use of real-world data. With the introduction of an electronic toxicity scoring registration (based on the CTCAE), a more systematic recording of treatment related toxicity was implemented at the NKI in 2012 (53, 54). In **chapter 7,** data from the electronic registration of AET was used to validate the applicability of real-world data for the NTCP-models for AET of CCRT for NSCLC-patients, for the 2 sequential cohorts as described in **chapter 2**. We found that real-world data is a useful method to audit NTCP-models in clinical practice. This model should ideally be tested in several institutions. To further optimize NTCP models, patient reported outcomes (PROs) can be used, since PROs have shown to be an useful complement to improve precision and accuracy when comparing these to clinician reported outcomes alone (55, 56). To conclude, due to continuous improvement of radiotherapy techniques and schedules, a constant update of NTCP-models is crucial to adequately predict radiotherapy induced toxicities. The use of real-world data and PROs simplifies and accelerates quality assurance and provide tools to validate these NTCP-models.

Future Perspectives

Adaptive radiotherapy and artificial intelligence

The studies in **chapter 4 and 5** showed that tumor regression is frequently seen during treatment on CBCT. As already described in a previous paragraph, adaptive radiotherapy is a promising approach to account for tumor volume regression and other intra thoracic anatomical changes during treatment. Currently, adaptive radiotherapy is a time-consuming strategy due to the manual clinical effort needed to produce an adaptive plan in a short time period. Besides, in current clinical practice, the decision to make an adapted plan usually relies on the decision of the radiation oncologist and physicist, which is inherently subjective (57). Adaptive radiotherapy may benefit from the advances of artificial intelligence (AI). With the use of AI, sophisticated predictive models can be developed with observational data by a computer. Then, these models can assess complex relationships between data. Automatic segmentation based on deep learning is an example of a frequently used application developed by AI in radiotherapy treatment planning with the use of the RT-planning CT. With automatic segmentation, the delineation of OAR is accelerated since it is done automatically instead of manually. Besides, it decreases inter- and

intra-observer variability (58). The challenge is to make this automatic segmentation suitable for CBCT's, so that a new RT-planning CT is not mandatory to adapt radiotherapy treatment planning. Moreover, the use of AI in automated treatment planning is rapidly developing (59), which enables the opportunity to implement adaptive radiotherapy in clinical practice in the broader radiotherapy community, since for some departments the time consuming (manually) procedure of re-planning is currently a limiting factor for routine clinical implementation.

The introduction of magnetic resonance-guided radiation therapy (MRgRT) enables the use of imaging with superior soft tissue contrast without the use of ionizing radiation. This allows real-time imaging of the tumor and OAR before and during treatment, and combined with an online-adaptive workflow, online adaptation of the RT-planning is possible (60-62). MR-guided online adaptive radiotherapy (MRgART) improves visualization for image guided and adaptive radiotherapy compared to the image quality of CBCT. Further research to develop AI techniques in IGRT and MRgRT should be embraced to improve efficiency of adaptive radiotherapy in daily clinic.

Prediction modelling and radiomics

TNM-staging is the cornerstone in the classification of lung cancer, based on comprehensive evidence from (randomized) clinical studies and observational data (63). However, there is still a considerable variation in the treatment response among patients with identical lung cancer stages. The search for new biomarkers to improve current prediction models for a better patient selection is therefore essential. In recent years, knowledge on tumor heterogeneity is increasing (64), both between and within tumors, urging the need for further developing treatment options that can operate on an individual level rather than on a population level. One of the new promising fields that uses this tumor heterogeneity in prediction modelling, is radiomics. Radiomics is a method that extracts large amounts of features from radiographic medical images using data-characterization algorithms. These features are subsequently correlated with tumor characteristics and/or prognostic endpoints using advanced machine learning algorithms to develop computational prediction models (65, 66). All lung cancer patients undergo medical imaging, especially CT-imaging, subsequently making CT-based biomarkers attractive to optimize current prediction models for NSCLC-patients. Fornacon et al. (67) found 43 CT-image based articles in which the prognostic or predictive role of radiomics signatures in NSCLC-patients were described. The conclusion of this review was, that generally the

studies present a positive view of the potential for radiomics signatures to deliver personalized medicine. However, there are some limitations. The radiomics signatures associated with treatment outcome vary substantially between the different studies reported. There is not one specific radiomic signature identified to evaluate in larger multicenter studies. Besides, radiomics studies suffer from several technical and methodological limitation such as lack of biological and technical validation (67). This is illustrated by the external validation (68-70) of the radiomics signature of Aerts et al. (71). The subsequently performed study of Welch et al.(72) demonstrated that this radiomics signature was highly correlated with tumor volume rather than reflecting tumor heterogeneity. In recent years several studies on the limitation of radiomics studies were performed (67), and the awareness increases that standardization and transparency of technical and methodological aspects of radiomics studies are necessary to establish true progress in this research field. Finally, it is important that radiomics signatures are tested for clinical relevance at a multi institutional level. Incorporating radiomics signatures into clinical models, should improve the accuracy of these existing models for patients risk stratification.

Radiotherapy and the immune system

How can we further optimize treatment outcome? The immune system has an important role in tumor response and treatment outcome. It is well established that radiotherapy can activate the immune system by different mechanisms like immunogenic cell death, leading to host immune responses as well as local inflammatory responses. This is illustrated by the abscopal effect of radiotherapy (73). Besides its immune activating effect, radiotherapy can also suppress the immune system (74). This is, amongst other mechanisms, explained by destruction of mature circulating lymphocytes in the blood-flow or lymphocytes in the tumor-draining lymph nodes. This cell type exhibits DNA fragmentation already at low doses of radiation (<1 Gy) (75). The heart and many large blood vessels are situated within the thoracic region, subsequently leading to irradiation of the blood flow (and thus with mature lymphocytes) during lung cancer irradiation. Several studies identified that lymphocyte count is associated with treatment outcome in different solid cancers including NSCLC (76-81). The study of Contreras (78) found a worse OS in patients with a neutrophil to lymphocyte ratio (NLR) >10.5, four months post radiotherapy. An expected association between heart dose and NLR >10.5 was found in multivariate analysis. This substantiates that larger radiation fields expose more circulating

lymphocytes and neutrophils to a radiation dose and that this plausibly leads to more immune suppression leading consecutive to a worse treatment outcome. In addition, larger radiation fields include more often lymph nodes, leading to an increased radiation dose to lymphocytes as well. The effect of larger thoracic radiation fields is illustrated for example by the study of Tang (82). Tang et al. reported that larger GTV's were correlated with lower lymphocytes nadirs in NSCLC patients who were treated with definitive radiotherapy, regardless whether concurrent chemotherapy was administered. Moreover, a lower lymphocyte nadir and larger GTV volume were associated with worse OS in this study. These blood biomarkers (total lymphocyte count and neutrophil to lymphocyte ratio) have the advantage of being cheap and easily repeatable during treatment since they can be calculated using routine blood analysis. Since the first results are promising, ongoing research is needed to unravel the exact mechanism of immunosuppression during radiotherapy and to validate the value of lymphocyte count as predictive biomarker in LA-NSCLC. Hopefully in the future these blood biomarkers can refine current treatment outcome prediction models.

Optimizing radiotherapy by adding immunotherapy

As described in the previous paragraph, radiotherapy could, besides suppress, also stimulate the immune system (73). This immune stimulating effect nourished the theory that the combination of radiotherapy and immunotherapy might improve treatment outcome. Pre-clinical evidence showed that radiotherapy up-regulates death ligand 1 (PD-L1) expression in tumor cells (83). Durvalumab is a selective, high affinity, human immunoglobulin-G1 (IgG1) monoclonal antibody that blocks programmed PD-L1 binding to programmed death 1 (PD-1) and CD80, allowing T-cells to recognize and kill tumor cells (84). In the phase III Pacific study, randomization occurred between placebo and Durvalumab as consolidation therapy after CCRT in NSCLC patients (2, 3). Because of the improved OS and PFS in the Durvalumab-arm, Durvalumab is now standard of care after CCRT in responding patients. The results of the Pacific study generated new research questions and trials. One of these trials was the phase 1 study that addressed whether immunotherapy (Pembrolizumab) could be given concurrently with chemoradiation (85). The trial concluded that it was tolerable (no dose limiting toxic-effects) with a promising PFS of 69.7% at 1 year. Pembrolizumab is another monoclonal antibody that blocks PD-1. The Pembro-trial (86) investigated the effect of stereotactic radiotherapy (SBRT) on the response to

PD-1 blockade in patients with metastatic NSCLC by analyzing tumor response in non-irradiated lung cancer lesions. In this phase II study, metastatic NSCLC patients (unselected for PD-L1 status) with progression after chemotherapy, were randomized to receive treatment with Pembrolizumab, either after SBRT (3 x 8 Gy) to a single tumor site or without SBRT. Improvement of overall response was seen (18% vs 36%, p <0.10) in the experimental arm. However, the results did not meet the study predefined endpoints for meaningful clinical benefit. Other trials (87, 88) reported that the response rate of Pembrolizumab is dependent on the PD-L1 expression levels of the tumor. Therefore, the PD-L1 negative subgroup is expected to have influenced the results of the Pembro-trial (86). A currently ongoing multicenter study examining the activity of immunotherapy (L19-IL2) and SBRT in metastatic NSCLC is the phase II ImmunoSABR study (89). The expected activity is a systemic immune response preventing disease progression and resulting in an improvement of PFS. The ability that SBRT in combination with immunotherapy might provoke a systemic immune response to improve PFS is auspicious. These studies illustrate that radiotherapy and immunotherapy are a very promising combination with the potential to further improve treatment outcome for lung cancer patients.

Proton therapy and NTCP-modelling

Predicting the risk of AET enables us to take appropriate precautions, such as individualized patient information, hydration, tube feeding or dietary guidance and supplements. Accurate NTCP-models will help to select the ideal patients who might benefit from novel radiotherapy techniques such as proton therapy (90, 91). A phase III study (92) randomizing between IMRT and passive scattering proton therapy (PSPT), reported a significantly lower mean heart dose in the PSPT-arm. However, no significant differences in the mean lung dose and mean esophagus dose were achieved. In spite of the similar mean lung dose, PSPT reduced the low-dose bath (lung $V_{5\text{-}10}$), but exposed significantly larger volumes to higher doses (lung $V_{20\text{-}80}$). The primary end points of this study were radiation pneumonitis grade 3 and local failure. No significant differences in grade 3 radiation pneumonitis (IMRT 6.5%; PSPT 10.5%, p=0.537) and in local failure was reported (IMRT 10.9%; PSPT 10.5%, p=1.0). Intensity Modulated Proton Therapy (IMPT) is a new and more advanced technique compared to PSPT. IMPT has the ability to deliver a more conformal dose to the tumor and spare the nearby organs at risk even more compared to PSPT. But this can make IMPT more sensitive for patient and tumor movements and anatomical changes. The

currently ongoing RTOG 1308 phase III trial has as primary objective to compare OS, lymphopenia and cardiac toxicity of LA-NSCLC patients, who are randomized between IMRT and proton beam therapy (93). Secondary endpoints of this trial are 2-year PFS, grade ≥3 adverse events, quality of life and cost effectiveness. In this trial IMPT and isotoxic dose escalation (60 to 70 Gy) are allowed. This is important, because the potentially improved local control of dosimetric advantages in the proton-arm due to dose escalation by OAR sparing can be assessed. Hopefully this trial will contribute to our knowledge on the clinical benefit of IMPT compared to the widely used IMRT. The use of NTCP-models supports personalized radiotherapy. For example in patients with a low toxicity risk, dose escalation can be applied, and patient with a high toxicity risk can be selected for more conformal radiation techniques such as IMPT. Because of the limited availability of proton therapy in the Netherlands and high costs, it is important to select those patients that will benefit the most from this treatment. Therefore, in the Netherlands a so called "model based approach" is implemented, to decide which lung cancer patients should be selected for proton therapy (91). In this approach, NTCP models of radiation pneumonitis, acute esophagitis and mortality are used to estimate what the expected difference (ΔNTCP) in complication risk is between photons and protons. If this comparison reveals a considerable decrease of this complication risk, proton therapy is indicated. These NTCP-models are based on photon radiotherapy data, hence validation with proton radiotherapy data is essential in the future. In summary, new radiotherapy techniques such as IMPT might lead to an improved sparing of OAR and are therefore potentially suitable for dose escalation with improved outcome for the patient.

Conclusions

In the last decades big steps have been made in the treatment for LA-NSCLC. The studies presented in this thesis all contribute to the optimization of radiotherapy for LA-NSCLC patients to reduce toxicity while improving locoregional control. Several improvements in the personalized treatment of lung cancer patients are expected to be implemented within clinical practice in the coming years. Cooperation between different research areas such as pharmacology, biostatistics, artificial intelligence, radiology, medical physics and radiation oncology, is essential to achieve these improvements.

References

1. Auperin A, Le Pechoux C, Rolland E, Curran WJ, Furuse K, Fournel P, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-90.
2. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
3. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377(20):1919-29.
4. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16(2):187-99.
5. Hallqvist A, Bergstrom S, Bjorkestrand H, Svard AM, Ekman S, Lundin E, et al. Dose escalation to 84 Gy with concurrent chemotherapy in stage III NSCLC appears excessively toxic: Results from a prematurely terminated randomized phase II trial. Lung Cancer. 2018;122:180-6.
6. Belderbos J, Uitterhoeve L, van Zandwijk N, Belderbos H, Rodrigus P, van de Vaart P, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). Eur J Cancer. 2007;43(1):114-21.
7. Walraven I, van den Heuvel M, van Diessen J, Schaake E, Uyterlinde W, Aerts J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. Radiother Oncol. 2016;118(3):442-6.
8. Dieleman EMT, Uitterhoeve ALJ, van Hoek MW, van Os RM, Wiersma J, Koolen MGJ, et al. Concurrent daily Cisplatin and high dose radiotherapy in patients with stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2018.
9. van Diessen JN, Chen C, van den Heuvel MM, Belderbos JS, Sonke JJ. Differential analysis of local and regional failure in locally advanced non-small cell lung cancer patients treated with concurrent chemoradiotherapy. Radiother Oncol. 2016;118(3):447-52.
10. 1Schytte T, Nielsen TB, Brink C, Hansen O. Pattern of loco-regional failure after definitive radiotherapy for non-small cell lung cancer. Acta Oncol. 2014;53(3):336-41.
11. Jouglar E, Isnardi V, Goulon D, Segura-Ferlay C, Ayadi M, Dupuy C, et al. Patterns of locoregional failure in locally advanced non-small cell lung cancer treated with definitive conformal radiotherapy: Results from the Gating 2006 trial. Radiother Oncol. 2018;126(2):291-9.
12. 1van Diessen JNA, Kwint M, Sonke JJ, Walraven I, Stam B, de Langen AJ, et al. Safety and efficacy of reduced dose and margins to involved lymph node metastases in locally advanced NSCLC patients. Radiother Oncol. 2019.
13. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.

14. Zhang TW, Snir J, Boldt RG, Rodrigues GB, Louie AV, Gaede S, et al. Is the Importance of Heart Dose Overstated in the Treatment of Non-Small Cell Lung Cancer? A Systematic Review of the Literature. Int J Radiat Oncol Biol Phys. 2019;104(3):582-9.
15. Cannon DM, Mehta MP, Adkison JB, Khuntia D, Traynor AM, Tome WA, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013;31(34):4343-8.
16. Kong FM, Ten Haken RK, Schipper M, Frey KA, Hayman J, Gross M, et al. Effect of Midtreatment PET/CT-Adapted Radiation Therapy With Concurrent Chemotherapy in Patients With Locally Advanced Non-Small-Cell Lung Cancer: A Phase 2 Clinical Trial. JAMA Oncol. 2017;3(10):1358-65.
17. Landau DB, Hughes L, Baker A, Bates AT, Bayne MC, Counsell N, et al. IDEAL-CRT: A Phase 1/2 Trial of Isotoxic Dose-Escalated Radiation Therapy and Concurrent Chemotherapy in Patients With Stage II/III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1367-77.
18. van Baardwijk A, Reymen B, Wanders S, Borger J, Ollers M, Dingemans AM, et al. Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer. Eur J Cancer. 2012;48(15):2339-46.
19. van Baardwijk A, Wanders S, Boersma L, Borger J, Ollers M, Dingemans AM, et al. Mature results of an individualized radiation dose prescription study based on normal tissue constraints in stages I to III non-small-cell lung cancer. J Clin Oncol. 2010;28(8):1380-6.
20. Study of Positron Emission Tomography and Computed Tomography in Guiding Radiation Therapy in Patients With Stage III Non-small Cell Lung Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT01507428.
21. Dose Escalation by Boosting Radiation Dose Within the Primary Tumor Using FDG-PET-CT Scan in Stage IB, II and III NSCLC (PET Boost). Available online: https://clinicaltrials.gov/ct2/show/NCT01024829.
22. van Diessen J, De Ruysscher D, Sonke JJ, Damen E, Sikorska K, Reymen B, et al. The acute and late toxicity results of a randomized phase II dose-escalation trial in non-small cell lung cancer (PET-boost trial). Radiother Oncol. 2019;131:166-73.
23. https://clinicaltrials.gov/ct2/show/NCT02473133.
24. https://clinicaltrials.gov/ct2/show/NCT02788461.
25. Group NM-AC. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol. 2008;26(28):4617-25.
26. De Ruysscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol. 2012;7(10):1547-55.
27. Gomez DR, Tang C, Zhang J, Blumenschein GR, Jr., Hernandez M, Lee JJ, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37(18):1558-65.

28. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019;393(10185):2051-8.
29. Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020;21(1):e18-e28.
30. Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst. 2017;109(9).
31. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018;4(1):e173501.
32. E²-RADIatE: EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe (E²-RADIatE). Available online: https://clinicaltrials.gov/ct2/show/NCT03818503.
33. Dingemans AC, Hendriks LEL, Berghmans T, Levy A, Hasan B, Faivre-Finn C, et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. J Thorac Oncol. 2019;14(12):2109-19.
34. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157-66.
35. Palma DA, Olson R, Harrow S, Correa RJM, Schneiders F, Haasbeek CJA, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): study protocol for a randomized phase III trial. BMC Cancer. 2019;19(1):816.
36. Sonke JJ, Zijp L, Remeijer P, van Herk M. Respiratory correlated cone beam CT. Med Phys. 2005;32(4):1176-86.
37. Britton KR, Starkschall G, Liu H, Chang JY, Bilton S, Ezhil M, et al. Consequences of anatomic changes and respiratory motion on radiation dose distributions in conformal radiotherapy for locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2009;73(1):94-102.
38. Kavanaugh J, Hugo G, Robinson CG, Roach MC. Anatomical Adaptation-Early Clinical Evidence of Benefit and Future Needs in Lung Cancer. Semin Radiat Oncol. 2019;29(3):274-83.
39. Tennyson N, Weiss E, Sleeman W, Rosu M, Jan N, Hugo GD. Effect of variations in atelectasis on tumor displacement during radiation therapy for locally advanced lung cancer. Adv Radiat Oncol. 2017;2(1):19-26.
40. Berkovic P, Paelinck L, Lievens Y, Gulyban A, Goddeeris B, Derie C, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer, can we predict when and for whom? Acta Oncol. 2015;54(9):1438-44.
41. Ramella S, Fiore M, Silipigni S, Zappa MC, Jaus M, Alberti AM, et al. Local Control and Toxicity of Adaptive Radiotherapy Using Weekly CT Imaging: Results from the LARTIA Trial in Stage III NSCLC. J Thorac Oncol. 2017;12(7):1122-30.

42. Curran WJ, Jr., Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(19):1452-60.
43. Senan S, Brade A, Wang LH, Vansteenkiste J, Dakhil S, Biesma B, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2016;34(9):953-62.
44. Bral S, De Ridder M, Duchateau M, Gevaert T, Engels B, Schallier D, et al. Daily megavoltage computed tomography in lung cancer radiotherapy: correlation between volumetric changes and local outcome. Int J Radiat Oncol Biol Phys. 2011;80(5):1338-42.
45. Jabbour SK, Kim S, Haider SA, Xu X, Wu A, Surakanti S, et al. Reduction in Tumor Volume by Cone Beam Computed Tomography Predicts Overall Survival in Non-Small Cell Lung Cancer Treated With Chemoradiation Therapy. Int J Radiat Oncol Biol Phys. 2015;92(3):627-33.
46. Wald P, Mo X, Barney C, Gunderson D, Haglund AK, Bazan J, et al. Prognostic Value of Primary Tumor Volume Changes on kV-CBCT during Definitive Chemoradiotherapy for Stage III Non-Small Cell Lung Cancer. J Thorac Oncol. 2017;12(12):1779-87.
47. Amugongo LM, Vasquez Osorio E, Green AF, Cobben D, van Herk M, McWilliam A. Identification of patterns of tumour change measured on CBCT images in NSCLC patients during radiotherapy. Phys Med Biol. 2020.
48. O'Rourke N, Roque IFM, Farre Bernado N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev. 2010(6):CD002140.
49. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv1-iv21.
50. Choy H, LaPorte K, Knill-Selby E, Mohr P, Shyr Y. Esophagitis in combined modality therapy for locally advanced non-small cell lung cancer. Semin Radiat Oncol. 1999;9(2 Suppl 1):90-6.
51. Wijsman R, Dankers F, Troost EGC, Hoffmann AL, van der Heijden E, de Geus-Oei LF, et al. Comparison of toxicity and outcome in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy using IMRT or VMAT. Radiother Oncol. 2017;122(2):295-9.
52. Zhang J, Yu XL, Zheng GF, Zhao F. Intensity-modulated radiotherapy and volumetric-modulated arc therapy have distinct clinical advantages in non-small cell lung cancer treatment. Med Oncol. 2015;32(4):94.
53. Akbarov A, Williams R, Brown B, Mamas M, Peek N, Buchan I, et al. A Two-stage Dynamic Model to Enable Updating of Clinical Risk Prediction from Longitudinal Health Record Data: Illustrated with Kidney Function. Stud Health Technol Inform. 2015;216:696-700.
54. Tamblyn R, Girard N, Dixon WG, Haas J, Bates DW, Sheppard T, et al. Pharmacosurveillance without borders: electronic health records in different countries can be used to address important methodological issues in estimating the risk of adverse events. J Clin Epidemiol. 2016;77:101-11.
55. Atkinson TM, Li Y, Coffey CW, Sit L, Shaw M, Lavene D, et al. Reliability of adverse symptom event reporting by clinicians. Qual Life Res. 2012;21(7):1159-64.

56. Trotti A, Colevas AD, Setser A, Basch E. Patient-reported outcomes and the evolution of adverse event reporting in oncology. J Clin Oncol. 2007;25(32):5121-7.
57. Boejen A, Vestergaard A, Hoffmann L, Ellegaard MB, Rasmussen AM, Moller D, et al. A learning programme qualifying radiation therapists to manage daily online adaptive radiotherapy. Acta Oncol. 2015;54(9):1697-701.
58. Schipaanboord B, Boukerroui D, Peressutti D, van Soest J, Lustberg T, Dekker A, et al. An Evaluation of Atlas Selection Methods for Atlas-Based Automatic Segmentation in Radiotherapy Treatment Planning. IEEE Trans Med Imaging. 2019;38(11):2654-64.
59. Wang C, Zhu X, Hong JC, Zheng D. Artificial Intelligence in Radiotherapy Treatment Planning: Present and Future. Technol Cancer Res Treat. 2019;18:1533033819873922.
60. Chin S, Eccles CL, McWilliam A, Chuter R, Walker E, Whitehurst P, et al. Magnetic resonance-guided radiation therapy: A review. J Med Imaging Radiat Oncol. 2020;64(1):163-77.
61. Lagendijk JJ, Raaymakers BW, Van den Berg CA, Moerland MA, Philippens ME, van Vulpen M. MR guidance in radiotherapy. Phys Med Biol. 2014;59(21):R349-69.
62. van Timmeren JE, Chamberlain M, Krayenbuehl J, Wilke L, Ehrbar S, Bogowicz M, et al. Treatment plan quality during online adaptive re-planning. Radiat Oncol. 2020;15(1):203.
63. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
64. Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature. 2013;501(7467):338-45.
65. Parikh R, Mathai A, Parikh S, Chandra Sekhar G, Thomas R. Understanding and using sensitivity, specificity and predictive values. Indian J Ophthalmol. 2008;56(1):45-50.
66. Yip SS, Aerts HJ. Applications and limitations of radiomics. Phys Med Biol. 2016;61(13):R150-66.
67. Fornacon-Wood I, Faivre-Finn C, O'Connor JPB, Price GJ. Radiomics as a personalized medicine tool in lung cancer: Separating the hope from the hype. Lung Cancer. 2020;146:197-208.
68. de Jong EEC, van Elmpt W, Rizzo S, Colarieti A, Spitaleri G, Leijenaar RTH, et al. Applicability of a prognostic CT-based radiomic signature model trained on stage I-III non-small cell lung cancer in stage IV non-small cell lung cancer. Lung Cancer. 2018;124:6-11.
69. Grossmann P, Stringfield O, El-Hachem N, Bui MM, Rios Velazquez E, Parmar C, et al. Defining the biological basis of radiomic phenotypes in lung cancer. Elife. 2017;6.
70. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol. 2014;32(26):2847-54.
71. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, Carvalho S, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun. 2014;5:4006.
72. Welch ML, McIntosh C, Haibe-Kains B, Milosevic MF, Wee L, Dekker A, et al. Vulnerabilities of radiomic signature development: The need for safeguards. Radiother Oncol. 2019;130:2-9.

73. Reynders K, Illidge T, Siva S, Chang JY, De Ruysscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. Cancer Treat Rev. 2015;41(6):503-10.
74. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst. 2013;105(4):256-65.
75. Sellins KS, Cohen JJ. Gene induction by gamma-irradiation leads to DNA fragmentation in lymphocytes. J Immunol. 1987;139(10):3199-206.
76. Campian JL, Ye X, Brock M, Grossman SA. Treatment-related lymphopenia in patients with stage III non-small-cell lung cancer. Cancer Invest. 2013;31(3):183-8.
77. Grossman SA, Ellsworth S, Campian J, Wild AT, Herman JM, Laheru D, et al. Survival in Patients With Severe Lymphopenia Following Treatment With Radiation and Chemotherapy for Newly Diagnosed Solid Tumors. J Natl Compr Canc Netw. 2015;13(10):1225-31.
78. Contreras JA, Lin AJ, Weiner A, Speirs C, Samson P, Mullen D, et al. Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer. Radiother Oncol. 2018;128(3):498-504.
79. Thor M, Montovano M, Hotca A, Luo L, Jackson A, Wu AJ, et al. Are unsatisfactory outcomes after concurrent chemoradiotherapy for locally advanced non-small cell lung cancer due to treatment-related immunosuppression? Radiother Oncol. 2020;143:51-7.
80. Zhao Q, Chen G, Ye L, Shi S, Du S, Zeng Z, et al. Treatment-duration is related to changes in peripheral lymphocyte counts during definitive radiotherapy for unresectable stage III NSCLC. Radiat Oncol. 2019;14(1):86.
81. Song X, Chen D, Yuan M, Wang H, Wang Z. Total lymphocyte count, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio as prognostic factors in advanced non-small cell lung cancer with chemoradiotherapy. Cancer Manag Res. 2018;10:6677-83.
82. Tang C, Liao Z, Gomez D, Levy L, Zhuang Y, Gebremichael RA, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. Int J Radiat Oncol Biol Phys. 2014;89(5):1084-91.
83. Zhang P, Su DM, Liang M, Fu J. Chemopreventive agents induce programmed death-1-ligand 1 (PD-L1) surface expression in breast cancer cells and promote PD-L1-mediated T cell apoptosis. Mol Immunol. 2008;45(5):1470-6.
84. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol. 2015;33(17):1974-82.
85. Jabbour SK, Berman AT, Decker RH, Lin Y, Feigenberg SJ, Gettinger SN, et al. Phase 1 Trial of Pembrolizumab Administered Concurrently With Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. JAMA Oncol. 2020.
86. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol. 2019.
87. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced NonSmall-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.

88. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019;37(7):537-46.
89. https://clinicaltrials.gov/ct2/show/NCT03705403.
90. Widder J, van der Schaaf A, Lambin P, Marijnen CA, Pignol JP, Rasch CR, et al. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. Int J Radiat Oncol Biol Phys. 2016;95(1):30-6.
91. Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol. 2013;107(3):267-73.
92. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2018;36(18):1813-22.
93. https://clinicaltrials.gov/ct2/show/NCT01993810.

APPENDICES

Summary

Over 13,000 patients are yearly diagnosed with lung cancer in the Netherlands. Surgery is treatment of choice, but only 20% of patients qualify for a curative resection. About 25% of the patients are diagnosed with locally advanced non-small cell lung cancer (LA-NSCLC). The standard treatment of this stage is concurrent chemoradiotherapy (CCRT) with adjuvant immunotherapy in patients without progression after CCRT. This is an intensive treatment and associated with toxicities, such as dysphagia. Despite the curative intent of CCRT for LA-NSCLC patients, overall survival (OS) is still poor. More personalized treatment is needed, in which treatment outcomes can hopefully be improved and toxicity can be more accurately predicted and reduced.

The purpose of this thesis was to evaluate strategies to improve the radiotherapy for LA-NSCLC patients. Focus was on different aspects of the treatment. The specific dose prescription for LA-NSCLC patients was optimized by differentiating the dose to the primary tumor and involved mediastinal lymph nodes to improve treatment outcome and to reduce toxicities. Further, the patient selection for the treatment of oligometastatic disease was analyzed. A clear and practical decision support system was introduced in the clinical practice to optimize the workflow for image guided radiotherapy with ConeBeam-CT (CBCT). Besides, the imaging data of tumor volume regression during treatment detected on CBCT was associated with treatment outcome. Finally, the normal tissue complication probability (NTCP) model to predict the risk of acute esophagus toxicity was optimized.

Part I Dose prescription and patient selection

In the Netherlands Cancer Institute patients with LA-NSCLC are treated with a (mild) hypofractionated radiotherapy schedule (24x2.75 Gy) compared to a conventional schedule of 60 Gy in 30 fractions. This hypofractionated schedule shortens the overall treatment time from 6 till 5 weeks reducing tumor cell repopulation during the course of treatment. Recent studies showed that dose escalation with prolonged overall treatment time might lead to a worse overall survival (OS) and increased toxicity compared to the conventional scheme. Possible causes of this poorer OS are dose to the heart, extended overall treatment time and higher grade ≥3 toxicities (e.g. dysphagia). Concurrent chemoradiation for LA-NSCLC causes severe dysphagia due to the radiation dose to the mediastinal lymphadenopathy and the proximity of the esophagus. Previous research showed that the regional failure rate is lower than

local failure, due to the lower tumor volume of the involved mediastinal lymph nodes. Reducing the dose to the mediastinum might reduce these severe toxicity rates. Due to improved position verification methods with image guidance radiotherapy techniques, the margins for the primary tumor and involved lymph nodes were reduced in our institute, which can also decrease the toxicity. In **chapter 2** an observational study is described where dose-reduction to the lymph nodes as well as a margin reduction in 2 consecutive cohorts of LA-NSCLC patients treated with (chemo) radiotherapy were analyzed. The reference-cohort (N=170) received the same dose of 70 Gy (24x2.75Gy, $EQD2_{10}$) to the involved lymph nodes and primary tumor, while the reduction-cohort (N=138) received 24x2.42Gy (which is 60Gy; $EQD2_{10}$) to the involved lymph nodes. With 60 Gy instead of 70 Gy to the involved mediastinal lymph nodes, the acute grade 3 dysphagia and grade 3 pulmonary toxicity decreased significantly from 12.9% to 3.6% and 4.1% versus 0%, respectively. The regional failure rates were comparable. The median OS was significantly different: 26 months for the reference-cohort versus 35 months for the dose reduction-cohort. The conclusions of this study were that a differentiated dose to primary tumour and lymph nodes using a hypofractionated regimen is a safe treatment strategy with very low toxicity for LA-NSCLC patients. Nowadays these inhomogeneous dose prescriptions for the primary tumor and lymph nodes, as well as the reduced margins due to the daily online CBCT position verification, are standard care in current clinical practice in the Netherlands Cancer Institute.

In current practice patients with ≤ 5 metastases are considered as having oligometastatic disease. Evidence is growing that a radical treatment of the primary tumor as well all the metastases, leads to an improved progression free survival (PFS) and OS for these oligometastatic NSCLC patients. In **chapter 3** the PFS and OS is described of a cohort study of 91 patients with synchronous oligometastatic NSCLC who were treated with a radical intent. The PFS of this cohort was 14 months and the OS 32 months. The 1- and 2-year OS rates were 85% and 58% and the 1- and 2-year PFS rates were 55% and 27%, respectively. The conclusion of this study was that a radical local treatment of a selected group of NSCLC patients with good performance status presenting with synchronous oligometastatic disease resulted in favorable long-term PFS and OS. In current clinical practice in our institute, patients with oligometastatic disease are discussed in a multidisciplinary tumor board, and when feasible, a radical treatment is advised.

Part II Image Guided Radiotherapy

The overall treatment time of concurrent chemoradiation is about 5 to 6 weeks. In radiotherapy, it is generally assumed that the anatomy of the patient is stable during this treatment course. However, during the 5-6 weeks course of lung radiotherapy several anatomical changes may occur, such as increasing/decreasing atelectasis, infiltrative changes, tumor progression or regression and pleural effusion. With the introduction of advanced image-guided systems like kilo voltage (kV) CBCT, we have the ability to visualize the tumor and organs at risk in three dimensions just before, during and/or after each fraction. These CBCT is primarily used to minimize target misalignment and setup error. In clinical practice repetitive CBCT's during treatment have made us aware of intra thoracic anatomical changes (ITACs) during the course of a radical treatment. The aim of the study described in **chapter 4** was to quantify the ITAC's during the radiotherapy course. A total of 1500 CBCT's of 177 patients were analyzed. Our decision support system: "the traffic-light protocol", was retrospectively applied to all of these CBCT-scans. The traffic-light protocol has three urgency levels: red (considerable impact on dose distribution), orange (moderate impact on dose distribution) and green (negligible impact on dose distribution). In 72% of the patients ITAC's were observed with a maximum level of red, orange and green in 12%, 36% and 24% respectively. Fourteen patients (8%) required a new planning CT-scan and an adapted treatment plan to account for anatomical changes. Types of observed ITACs were, evident tumor regression (35%), considerable tumor baseline shift (27%), changes in atelectasis (19%), tumor progression (10%), pleural effusion (6%) and infiltrative changes (3%). This decision support system is currently used in our institute by the RTT's who analyze the CBCT's during treatment.

Although concurrent chemoradiotherapy of NSCLC patients has a curative intent, OS remains poor. To distinguish between patients with better or worse OS, prediction models are used. Current prediction models mainly use baseline characteristics to predict treatment outcomes. An important step to improve these prediction models is to incorporate longitudinal data. The use of CBCT's during treatment resulted in an increase of available imaging data of tumor volume change during radiotherapy treatment. The aim of the study in **chapter 5** was to identify subgroups of LA-NSCLC patients showing tumor volume changes during CCRT and to investigate whether the identified subgroups are associated with treatment outcomes. In this study of 394 patients, 3 different subgroups of tumor volume change during treatment

were identified. Surprisingly, these subgroups did not differ in their risk of treatment outcomes, whereas baseline volume of the primary tumor was significantly associated with OS. Therefore, risk stratification at baseline might already be accurate enough in identifying the best treatment strategy for most patients. However, further research is needed to optimize current prediction models.

Part III Acute esophagus toxicity

Intensity Modulated Radiotherapy (IMRT) results in a more conformal dose distribution leading to increased organ sparing compared to 3D-conformal-radiotherapy (3DCRT). The change of radiotherapy technique from 3D-CRT to IMRT can influence the accuracy of dose volume parameters to predict toxicity. In **chapter 6** the dose-effect-relation between acute esophageal toxicity (AET) and dose-volume-parameters of the esophagus after IMRT and concurrent chemotherapy in 139 NSCLC patients were investigated. The outcome was compared to the clinically (at that time in our institute) used esophagus V35 (volume of the esophagus receiving ≥35 Gy) prediction model for grade ≥2 after radical 3D-CRT treatment. The conclusion of this study was that the incidence of AET did not differ between patients treated with IMRT or 3D-CRT. The V50 (volume of the esophagus receiving ≥50 Gy) turned out to predict grade ≥2 significantly better compared to the clinical V35-model. At present the V50 of the esophagus is used as planningsconstraint in clinical practice in the Netherlands Cancer Institute.

Data obtained from sources outside of randomized clinical trials are often referred to as 'real world data' (RWD). By introducing electronic toxicity registration within our institute, a more systematic and accurate recording of toxicity was implemented in clinical practice. The RWD collected from this electronic toxicity registration, can be used to audit normal tissue complication probability (NTCP) models. The dose reduction of the involved mediastinal lymph nodes as described in **chapter 2** might have impact on the NTCP-model to predict AET. The aim of the study described in **chapter 7** was to assess the validity of the RWD derived from the electronic toxicity registration and to show the feasibility of this registration to audit toxicity prediction models and dose constraints used in daily clinical practice. As a showcase, 2 NTCP-models (V50 and V60; volume of the esophagus receiving ≥50 Gy and ≥60 Gy) of AET for CCRT for NSCLC patients were used to validate the electronic toxicity registration of AET before/after dose de-escalation of the prescribed dose to the mediastinal lymph

nodes (chapter 2). Data of 217 patients were analyzed. The conclusions of this study were that the use of real world data provides a useful method for quality assurance and for validation of NTCP-models in clinical practice. Both V50 and V60 NTCP-models showed moderate accuracy to predict acute esophageal toxicity in NSCLC patients. For clinical practice, the V50 seems to be the most stable dose volume parameter without compromising safety and efficacy after dose de-escalation.

Finally, chapter **8** provides the general discussion of this thesis.

Nederlandse Samenvatting

In Nederland worden jaarlijks meer dan 13000 patiënten gediagnosticeerd met longkanker. De voorkeursbehandeling voor longkanker is een operatie, echter in de praktijk komt slechts ongeveer 20% van de longkankerpatiënten in aanmerking voor een operatieve behandeling. Rond de 25% van de patiënten wordt gediagnosticeerd met een lokaal gevorderd niet kleincellige vorm van longkanker (LA-NSCLC). De standaardbehandeling voor dit stadium van ziekte is gelijktijdige chemotherapie en radiotherapie (chemoradiatie), met aansluitend immunotherapie indien de patiënt goed reageert op de gelijktijdige chemoradiatie. Dit is een hele intensieve behandeling die gepaard gaat met bijwerkingen zoals vermoeidheid en pijn met slikken (dysfagie). Hoewel het doel van deze behandeling genezing is, blijkt de overleving vaak slecht. Meer gepersonaliseerde zorg is nodig, waarbij bijwerkingen nauwkeuriger voorspeld kunnen worden en de behandeluitkomsten hopelijk verbeterd kunnen worden.

Het doel van het onderzoek, beschreven in dit proefschrift, was het evalueren van verschillende strategieën om de bestralingsbehandeling voor LA-NSCLC-patiënten te optimaliseren.

De nadruk lag op verschillende aspecten van deze behandeling. Het dosisvoorschrift voor de radiotherapie behandeling van LA-NSCLC-patiënten werd geoptimaliseerd door de dosis op de aangedane lymfeklieren en de primaire tumor te differentiëren teneinde de bijwerkingen te verminderen en de behandeluitkomst te verbeteren. Tevens werd de selectie voor patiënten met oligometastatische ziekte (beperkt aantal uitzaaiingen) die in aanmerking komen voor een radicale behandeling geanalyseerd. Om de werkwijze van beeld gestuurde radiotherapie met ConeBeam-CT (CBCT) te optimaliseren, werd er een praktisch en duidelijk beslissingsprotocol geïntroduceerd in de klinische praktijk. Daarnaast werd de beeldvormende data van tumor volume afname tijdens de behandeling, gedetecteerd op de CBCT, geassocieerd met behandeluitkomst. Als laatste werd het normale weefsel complicatie risico-model (normal tissue complication probability model: NTCP-model) voor radiatie oesophagitis (door bestraling geïnduceerde ontsteking van de slokdarm) geoptimaliseerd.

In **hoofdstuk 1** is een algemene introductie van de epidemiologie, stadiering en behandeling van longkanker beschreven. Verder worden in dit hoofdstuk de verschillende onderwerpen van dit proefschrift uitgelegd; radiotherapie technieken, oligometastasen in NSCLC, beeld gestuurde radiotherapie en slokdarm toxiciteit door radiotherapie.

Deel I. Dosis voorschriften en patiënten selectie

In het Antoni van Leeuwenhoek ziekenhuis worden patiënten met LA-NSCLC behandeld met een mild gehypofractioneerd bestralingsschema (24x2.75 Gy), in vergelijking met het conventionele schema van 30x2 Gy. Dit gehypofractioneerde bestralingsschema verkort de totale behandelduur van 6 naar 5 weken. Uit recente studies kan worden opgemaakt dat dosis escalatie in combinatie met een verlengde behandelduur, mogelijk leidt tot een slechtere overleving en meer toxiciteit, in vergelijking met het conventionele schema. Mogelijke verklaringen voor dit overlevingsverschil zijn bestralingsdosis op het hart, verlenging van de behandelduur en meer ernstige bijwerkingen (zoals slikklachten). Gelijktijdige chemo- en radiotherapie voor LA-NSCLC kan ernstige slikklachten geven door een bestraling geïnduceerde ontsteking van het slijmvlies van de slokdarm. Dit is het gevolg van de bestralingsdosis op de aangedane lymfeklieren in het gebied tussen de longen (mediastinum) en de nabijheid van de slokdarm. Voorafgaand onderzoek heeft uitgewezen dat regionale (lymfklier) recidieven minder vaak voorkomen dan recidieven van de primaire tumor, doordat het tumor volume van deze lymfeklieren vaak kleiner is dan dat van de primaire tumor. Door de dosis op deze aangedane lymfeklieren in het mediastinum te verlagen, wordt de dosis op de slokdarm ook verlaagd en kan daarmee mogelijk het risico op deze slikklachten verminderd worden. Door verbeterde positie verificatie methoden met beeld gestuurde radiotherapie zijn recentelijk de bestralingsmarges voor de primaire tumor en de aangedane lymfeklieren verkleind in ons instituut. Deze marge verkleining kan ook zorgen voor afname van toxiciteit. In **hoofdstuk 2** wordt een observationele studie beschreven waarin de dosis op de aangedane lymfeklieren is verlaagd alsmede de marges voor het planning-doelvolume (PTV) werden verkleind in 2 opeenvolgende cohorten voor LA-NSCLC-patiënten, die werden behandeld met (chemo)radiotherapie. Het referentie cohort (N=170) ontving dezelfde dosis van 24x2.75Gy (70 Gy; $EQD2_{10}$) op de aangedane lymfeklieren en de primaire tumor, terwijl het dosis reductie cohort (N=138) 24x2.42Gy (60Gy; $EQD2_{10}$) ontving op de aangedane lymfeklieren. De graad 3 slikklachten en long bijwerkingen (hoesten, kortademigheid en bestralingslongontsteking) namen significant af in het dosis reductie cohort van 12.9% naar 3.6% en 4.1% naar 0%, respectievelijk. Het aantal regionale recidieven was vergelijkbaar. De mediane overleving was significant beter in het dosis reductie cohort; 26 maanden in het referentie cohort i.v.m. 35 maanden in het dosis reductie cohort. De conclusie van deze studie was dat een dosis reductie op de aangedane lymfeklieren met een gehypofractioneerd bestralingsschema veilig is met

beperkte toxiciteit voor LA-NSCLC-patiënten. Tegenwoordig is dit gedifferentieerde dosisschema voor de primaire tumor en lymfeklieren, de standaardbehandeling in het Antoni van Leeuwenhoek ziekenhuis.

In de huidige klinische praktijk worden patiënten met ≤ 5 uitzaaiingen beschouwd als oligometastatische ziekte. Er komt steeds meer bewijs dat een radicale behandeling van de primaire tumor en alle uitzaaiingen een betere ziektevrije overleving en betere overleving geven voor deze oligo-gemetastaseerde NSCLC-patiënten. In **hoofdstuk 3** worden de resultaten van een cohortstudie van 91 patiënten met oligo-gemetastaseerd NSCLC beschreven. In deze studie is de ziektevrije overleving en totale overleving geanalyseerd van patiënten die met een radicale intentie zijn behandeld. De ziektevrije overleving van dit cohort was 14 maanden en de totale overleving was 32 maanden. De 1- en 2-jaar overleving was 85% en 58% en de 1- en 2-jaar ziektevrije overleving was 55% en 27%. De conclusie van deze studie was dat een radicale behandeling in een selecte groep van NSCLC patiënten met een goede conditie en die zich presenteren met synchrone oligometastatische ziekte een gunstige ziektevrije overleving en totale overleving geeft. In de huidige klinische praktijk worden in ons instituut patiënten met oligo-gemetastaseerde ziekte besproken in een multidisciplinair overleg en wordt, wanneer haalbaar, een radicale behandeling geadviseerd.

Deel II. Beeld gestuurde radiotherapie

De behandelduur van gelijktijdige chemoradiatie ligt gemiddeld tussen de 5 en 6 weken. In het algemeen wordt aangenomen dat de anatomie van de patiënt niet verandert gedurende deze behandelperiode. Regelmatig treden er tijdens deze 5-6 weken van behandeling toch anatomische veranderingen op, zoals toename/afname van atelectase, infiltratieve veranderingen, pleuravocht, tumorgroei of juist tumorafname. Met de komst van geavanceerde beeld gestuurde technieken zoals kilo voltage (KV) ConeBeam computer tomografie (CBCT), werd het mogelijk om de tumor en de organen rondom de tumor in beeld te brengen in 3 dimensies vlak voor, tijdens en/of na elke bestralingsfractie. Het primaire doel van deze CBCT is om de inwendige positie van de tumor te controleren en zo nodig de patiënt positie hierop aan te passen. In de praktijk zorgden deze herhaaldelijke CBCT's er tevens voor dat meer anatomische intra thoracale veranderingen werden geobserveerd (intra thoracic anatomical changes = ITAC) tijdens de bestralingsbehandeling. Het doel van

de studie, beschreven in **hoofdstuk 4** was om te kwantificeren hoe vaak deze ITAC's plaatsvinden tijdens de bestralingsbehandeling. In totaal werden 1500 CBCT's van 177 patiënten beoordeeld. Het beslissingsprotocol van ons instituut 'het Stoplichtprotocol', werd retrospectief toegepast op al deze CBCT's. Dit stoplichtprotocol heeft 3 niveaus: rood (grote invloed op dosisverdeling), oranje (matige invloed op dosisverdeling) en groen (verwaarloosbare invloed op dosisverdeling). In 72% van de patiënten werd een ITAC geobserveerd, met een maximaal niveau van rood, oranje of groen in respectievelijk 12%, 36% en 24% van de gevallen. Veertien patiënten (8%) hadden een nieuwe planningsCT en een aangepast bestralingsplan nodig om te corrigeren voor deze anatomische veranderingen. De verschillende ITAC's die werden waargenomen zijn: evidente tumor afname (35%), tumor baseline shift (27%), veranderingen in atelectase (19%), tumor progressie (10%), pleuravocht (6%) en ontstekingsbeeld (3%). Dit stoplichtprotocol wordt momenteel in de klinische praktijk gebruikt in ons instituut door de radiotherapeutisch laboranten die de CBCT beoordelen tijdens de bestralingsbehandeling.

Hoewel het doel van gelijktijdige chemoradiotherapie voor NSCLC-patiënten genezing is, blijft de overleving slecht. Om onderscheid te kunnen maken tussen patiënten met betere of slechtere overleving, worden predictiemodellen gebruikt. De huidige predictiemodellen gebruiken hoofdzakelijk tumor- en patiënt-karakteristieken voor start van de behandeling om behandeluitkomsten te voorspellen. Een belangrijke stap voorwaarts om deze modellen te verbeteren, is het hierbij betrekken van longitudinale data. Het gebruik van CBCT's tijdens de behandeling heeft geleid tot een enorme toename van beeldvorming van tumorvolume veranderingen tijdens de bestralingsbehandeling. Het doel van de studie beschreven in **hoofdstuk 5** was om subgroepen van LA-NSCLC-patiënten te identificeren die tumorvolume veranderingen tijdens gelijktijdige chemoradiotherapie lieten zien, en vervolgens te analyseren of deze subgroepen geassocieerd zijn met behandeluitkomsten. In deze studie van 394 patiënten, werden drie verschillende subgroepen van tumorvolume veranderingen geïdentificeerd. Er bleek geen significant verschil in behandeluitkomst te bestaan tussen deze groepen. Het tumorvolume bij start van de behandeling was wel significant voorspellend voor een slechtere overleving. Derhalve is risico stratificatie bij start van behandeling mogelijk al nauwkeurig genoeg om voor de meeste patiënten de beste behandelstrategie te bepalen. Het is evident dat verder onderzoek nodig is om de huidige predictiemodellen verder te verbeteren.

Deel III. Acute slokdarm toxiciteit

Intensiteit gemoduleerde radiotherapie (IMRT) zorgt voor een meer conformele dosis verdeling en daardoor betere sparing van gezonde organen in vergelijking met 3D conformele radiotherapie (3D-CRT). Door de verandering van radiotherapie techniek van 3D-CRT naar IMRT kunnen de dosis volume parameters die het risico op bijwerkingen voorspellen, beïnvloed worden. In **hoofdstuk 6** werd onderzocht wat de dosis effect relatie is voor acute slokdarm toxiciteit bij IMRT in 139 LA-NSCLC-patiënten die behandeld werden met gelijktijdige chemoradiotherapie. De uitkomst werd vergeleken met het (op dat moment) in de kliniek gebruikte V35 predictie model van de slokdarm (volume van de slokdarm dat ≥35 Gy ontvangt) om graad ≥2 acute slokdarm toxiciteit te kunnen voorspellen met radicale radiotherapie middels 3D-CRT. De conclusie van deze studie was, dat de incidentie van acute slokdarm bijwerkingen niet verschilde tussen patiënten die behandeld waren met IMRT of 3D-CRT. De V50 (volume van de slokdarm dat ≥50 Gy ontvangt) bleek de beste dosimetrische voorspeller voor graad ≥3 acute slokdarm toxiciteit. Het V50 model was significant beter om graad ≥2 acute slokdarm toxiciteit te voorspellen dan het oude V35 model. Momenteel wordt het V50-model van de slokdarm gebruikt als planningsrestrictie in het Antoni van Leeuwenhoek ziekenhuis.

Data die niet uit gerandomiseerde studies afkomstig zijn, worden regelmatig geclassificeerd als 'real world data' (RWD). Door de introductie van het elektronische patiëntendossier in ons instituut, werd een nauwkeuriger en meer systematische manier van toxiciteitregistratie geïmplementeerd in de klinische praktijk. De RWD verkregen uit deze registratie, kunnen gebruikt worden voor het valideren van NTCP-modellen. De dosis reductie zoals beschreven in **hoofdstuk 2** voor de behandeling van NSCLC-patiënten, kan de NTCP-modellen voor acute slokdarm toxiciteit hebben beïnvloed. Het doel van de studie in **hoofdstuk 7** was om te toetsen of de RWD, verkregen uit de elektronische toxiciteit registratie, gebruikt kunnen worden om NTCP-modellen te toetsen die in de dagelijkse klinische praktijk worden gebruikt. Als een showcase werd het NTCP-model voor acute slokdarm toxiciteit bij gelijktijdige chemoradiatie voor NSCLC-patiënten gebruikt om de validiteit van de elektronische toxiciteit registratie van acute slokdarm toxiciteit voor/na de de-escalatie van de radiotherapie dosis op de aangedane lymfeklieren (**hoofdstuk 2**) te analyseren. In deze studie werden data van 217 patiënten geanalyseerd. De conclusie van deze studie was dat het gebruik van RWD een geschikte methode is voor kwaliteitsdoeleinden en

voor validatie van NTCP-modellen in de klinische praktijk. Zowel de V50 als de V60 (volume van de slokdarm dat ≥50 Gy en ≥60 Gy ontvangt) NTCP-modellen lieten een redelijke nauwkeurigheid zien om acute slokdarm toxiciteit te voorspellen in NSCLC-patiënten. Voor de klinische praktijk kwam de V50 er als meest robuuste voorspeller uit na de dosis de-escalatie.

Tot slot, in **hoofdstuk 8** wordt een algemene discussie van dit proefschrift gegeven.

List of Publications

J. Belderbos, D. De Ruysscher, K. De Jaeger, F. Koppe, M. Lambrecht, Y. Lievens, E. Dieleman, J. Jaspers, J. Van Meerbeeck, J. Ubbels, **M. Kwint**, M. Kuenen, S. Deprez, M. De Ruiter, K. Sikorska, H. van Tinteren, S. Schagen.
Phase III randomized trial of Prophylactic Cranial Irradiation with or without Hippocampus Avoidance in SCLC (NCT01780675)
Journal of Thoracic Oncology, February 2021

van Diessen JNA, **Kwint MH**, Sonke JJ, Belderbos JSA.
In response to Park, et al.
Letter to the editor
Radiotherapy and Oncology, April 2020

Kwint MH, Walraven I, Verheij M, Sonke JJ, Belderbos JSA, Janssen TM.
The use of real-world evidence to audit normal tissue complication probability models for acute esophageal toxicity in non-small cell lung cancer patients.
Radiotherapy and Oncology, February 2020

Kwint M, Stam B, Proust-Lima C, Philipps V, Hoekstra T, Aalbersberg E, Rossi M, Sonke JJ, Belderbos J, Walraven I.
The prognostic value of volumetric changes of the primary tumor measured on Cone Beam-CT during radiotherapy for concurrent chemoradiation in NSCLC patients.
Radiotherapy and Oncology, February 2020

Kwint M, van Diessen JNA, Sonke JJ, Walraven I, Stam B, de Langen AJ, Knegjens B, Belderbos JSA.
Safety and efficacy of reduced dose and margins to involved lymph node metastases in locally advanced NSCLC patients.
Radiotherapy and Oncology, August, 2019

Stam B, **Kwint M**, Guckenberger M, Mantel F, Hope A, Giuliani M, Werner-Wasik M, Grills I, Sonke JJ, Belderbos J.
Subgroup Survival Analysis in Stage I-II NSCLC Patients With a Central Tumor Partly Treated With Risk-Adapted SBRT.
International Journal of Radiation, Oncology, Biology, Physics, January 2019

Walraven I, **Kwint M**, Belderbos J.
The Additional Prognostic Value of Tumor Volume Changes during Chemoradiotherapy in Patients with Stage III Non-Small Cell Lung Cancer.
Letter to the editor
Journal of Thoracic Oncology, September 2018

Dankers F, Wijsman R, Troost EGC, Tissing-Tan CJA, **Kwint MH**, Belderbos J, de Ruysscher D, Hendriks LE, de Geus-Oei LF, Rodwell L, Dekker A, Monshouwer R, Hoffman AL, Bussink J.
External validation of an NTCP model for acute esophageal toxicity in locally advanced NSCLC patients treated with intensity-modulated (chemo-)radiotherapy.
Radiotherapy and Oncology, September 2018

Deist TM, Dankers F, Valdes G, Wijsman R, Hsu IC, Oberije C, Lustberg T, van Soest J, Hoebers F, Jochems A, El Naqa I, Wee L, Morin O, Raleigh DR, Bots W, Kaanders JH, Belderbos J, **Kwint M**, Solberg T, Monshouwer R, Bussink J, Dekker A, Lambin P.
Machine learning algorithms for outcome prediction in (chemo)radiotherapy: An empirical comparison of classifiers.
Medical Physics, May 2018

Kwint M, Walraven I, Burgers S, Hartemink K, Klomp H, Knegjens J, Verheij M, Belderbos J.
Outcome of radical local treatment of non-small cell lung cancer patients with synchronous oligometastases.
Lung Cancer, October 2017

Kwint M, van den Heuvel M, Snijders D, Monkhorst K, Belderbos J.
Spontaneous Regression of Large Cell Carcinoma of the Lung, a Case Report.
Omics Journal of Radiology, October 2015

Kwint M, Conijn S, Schaake E, Knegjens J, Rossi M, Remeijer P, Sonke JJ, Belderbos J.
Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy.
Radiotherapy and Oncology, December 2014

M. Kwint, B. Doodeman, J. Belderbos en M. Verheij.
De rol van de Physician Assistant op de afdeling Radiotherapie.
Nederlands tijdschrift voor Oncologie, August 2013

Uyterlinde W, Chen C, **Kwint M**, de Bois J, Vincent A, Sonke JJ, Belderbos J, van den Heuvel M.
Prognostic parameters for acute esophagus toxicity in intensity modulated radiotherapy and concurrent chemotherapy for locally advanced non-small cell lung cancer.
Radiotherapy and Oncology, June 2013

Nijkamp J, Rossi M, Lebesque J, Belderbos J, van den Heuvel M, **Kwint M**, Uyterlinde W, Vogel W, Sonke JJ.
Relating acute esophagitis to radiotherapy dose using FDG-PET in concurrent chemo-radiotherapy for locally advanced non-small cell lung cancer.
Radiotherapy and Oncology, January 2013

Kwint M, Uyterlinde W, Nijkamp J, Chen C, de Bois J, Sonke JJ, van den Heuvel M, Knegjens J, van Herk M, Belderbos J.
Acute esophagus toxicity in lung cancer patients after intensity modulated radiation therapy and concurrent chemotherapy.
International Journal of Radiation, Oncology, Biology, Physics, October 2012

Dankwoord

Ja, en dan nu het dankwoord, het hoofdstuk van het proefschrift dat het meest gelezen wordt. Dit proefschrift was nooit tot stand gekomen zonder de hulp van velen. Graag wil ik iedereen die indirect of direct heeft bijgedragen aan het volbrengen van dit proefschrift heel erg bedanken. Een aantal mensen wil ik graag in het bijzonder bedanken.

Alle onderzoeken in dit proefschrift zijn gebaseerd op gegevens van patiënten. Ik wil alle patiënten heel erg bedanken voor het geven van toestemming voor het gebruik van de behandelgegevens. Zonder deze gegevens is er geen onderzoek mogelijk.

Mijn promotoren, prof dr. Verheij en prof. dr. Ir. Sonke.

Beste Marcel, doordat jij als hoofd van de afdeling het aandurfde om als een van de eerste radiotherapie afdelingen in Nederland met PA's te starten kreeg ik daarmee de kans om mijzelf verder te ontwikkelen binnen het AvL. Daarnaast wil ik je bedanken dat je mij de kans hebt gegeven om een PhD-traject te starten gecombineerd met patiënten zorg, zodat ik mij als onderzoeker verder kon ontwikkelen.

Beste Jan-Jakob, jou wil ik ook bedanken voor het geven van de mogelijkheid om een PhD-traject te starten. Daarnaast vond ik de research overleggen en commentaren op mijn manuscripten altijd erg leerzaam en inspirerend door jouw precieze blik. Dit heeft zeker bijgedragen aan mijn persoonlijke ontwikkeling als onderzoeker.

Mijn co-promotoren, dr. Belderbos en dr. Walraven,

Lieve Jose, in 2007 kwam in onder jouw vleugels terecht als PA. Jij hebt mij de klinische kant van het vak geleerd. Maar ook kwam ik via jou in aanraking met het doen van onderzoek. Het moment dat mijn afstudeeronderzoek een 'oral' presentatie werd op een internationaal congres, was achteraf gezien nog maar het begin. Ik vond dat toen hartstikke spannend maar ook heel erg leuk. Ik wil je heel erg bedanken voor het vertrouwen dat je in mij hebt en alle mogelijkheden die je me hebt gegeven.

Lieve Iris, nadat onze emigratie naar Zuid-Afrika toch niet door ging, ben jij epidemioloog geworden en ik PA. In 2015 kwam je weer terug in het AvL. En i.p.v. gesprekken over de uitspraak van Digestives op B1, gingen onze gesprekken nu vaak over onderzoek. Ik wil je bedanken voor de inspiratie die je hebt gegeven, waardoor we onder andere op R-vontuur gingen in Bordeaux om ons in LCMM te verdiepen.

Daarnaast heeft jouw goede kritische blik en begeleiding gezorgd dat ik veel geleerd heb.

Geachte leden van promotiecommissie, prof.dr. Slotman, prof.dr. Guckenberger, prof.dr. Bussink, prof.dr. Dingemans, prof.dr. Hoogeman, dr De Langen, dr. Peulen bedankt voor het beoordelen van mijn proefschrift. Thank you very much for assessing my dissertation.

Graag wil ik alle coauteurs danken voor hun waardevolle bijdragen aan de verschillende manuscripten.

Beste collega's van de afdeling radiotherapie; laboranten, afsprakenbureau, doktersassistenten, moulagemedewerkers, secretariaat, studie-ondersteuners, trial medewerkers, radiotherapeuten AIOS, fysica, PA's en alle overige medewerkers zonder jullie hadden we nooit alle data voor deze onderzoeken kunnen verzamelen. Door Corona spreken we elkaar allemaal wat minder op de werkvloer, maar wil ik graag toch de collegiale en prettige samenwerking met iedereen even benoemen.

De long research groep: Thanks everyone for the weekly meetings, in which we helped each other when we were stuck or needed motivation.

Maddalena, met jouw enorme energie en secure werkwijze ben jij een rots in de branding van de long research groep. Maar daarnaast ben je ook een hele fijne collega en heb ik genoten tijdens onze hike in Zwitserland.

Barbara, als ik advies nodig had kon ik altijd bij jou terecht om even te sparren. En dankzij jouw is Fogo de Chao nu een van mijn favoriete restaurants.

Beste collega's van het longteam (Joost, Rick, Judi, Jose, Renske, Monique en Saar), ik ben blij in zo'n fijn team te werken. Jullie wisten gelukkig af en toe op mijn rem te trappen als ik te veel hooi op mijn vork nam met de combinatie van een tweelingzwangerschap, promoveren en kliniek. Als team staan we voor elkaar klaar en daarnaast is gezelligheid ook belangrijk.

Lieve Heike, ik mis nog steeds jouw lach hier door de gangen van AvL. Helaas woon je nu wat verder weg dat we elkaar niet meer zo vaak spreken. We moeten post-Corona maar weer een congres afstemmen zodat we weer in een Cabrio kunnen cruisen of van Kaiseki kunnen genieten.

Lieve Judi, jij bent een hele fijne collega, die altijd goed de rust weet te bewaren. En daarnaast is het altijd leuk en gezellig om samen op culinaire ontdekkingstocht in Amsterdam te gaan. Geniet van je Indonesië avontuur maar zodra je terug bent kiezen we weer een goed restaurant uit om bij te kletsen.

Graag wil alle longartsen, thoraxchirurgen, radiologen, nucleair geneeskundigen, pathologen en verpleegkundig specialisten binnen de thorax oncologie werkgroep van het AvL bedanken voor de prettige samenwerking. Behalve samenwerking op het gebied van longkanker en onderzoek, komen de tweeling adviezen van Wieneke en Wanda ook goed van pas.

Lieve Wilma, hoeveel presentaties hebben we wel niet samen gegeven over CCRT. Dat jij een PhD ging doen was zeker een inspiratie voor mij. Ik vind het nog steeds jammer dat we niet meer samenwerken, maar gelukkig kom ik je nog af en toe in de gangen tegen.

Robin, samen zijn we in 2007 het PA-avontuur begonnen. Ik denk dat we mogen terugkijken op een geslaagd avontuur waarbij de ontdekking van de CheeseCake Factory ook zeker een hoogte punt was.

Lieve PA's (Robin, Barry, Sandra, Marcel, Gerbert, Corine, Hester en Cherita), ik ben heel dankbaar met jullie als PA-collega's. Een nieuwe functie en taakherschikking in de zorg is niet altijd even makkelijk, maar als PA-team weten we elkaar hierin elkaar te ondersteunen en motiveren. Daarnaast is het ook heel gezellig nu we met zijn allen (Corona-proof) op een kamer zitten.

Pink Ladies (Lilian, Marieke, Jeanette, Kati, Sabrina, Mariëlle, Margarita, Jitske, Linda en Viviënne) ondanks dat we (bijna) allemaal niet meer basketballen blijven we een hecht team. En zijn we naast basketballen nog beter in gezelligheid. Dit heeft geregeld gezorgd voor hilarische momenten en de nodige ontspanning.

Lieve sportvrienden, gelukkig kon ik bij jullie mijn passie voor sport en mijn energie kwijt.Phanos loopmaatjes (Gerard, Gadiza, Ritsert, Cindy, Kim, Sybren, Tjalling, Lieke, Lisa en Patricia) de ontelbare rondjes op de baan zorgden na een drukke werkdag vaak voor de broodnodige ontspanning. Maar ook van de duurloopjes en wielrenrondjes kan ik altijd erg genieten. Wanneer staat de volgende marathon op de planning? (gezien ik nu weer meer tijd heb)

Evert, je woont nu ook niet meer om de hoek maar we dan moeten we de provincie Utrecht maar eens op de racefiets verkennen (of met de bakfiets).

Lieve vrienden, ook al kan ik door onze drukke levens jullie niet altijd zo vaak zien als ik zou willen.

Angela en Goziëm, de gezellige etentjes houden we erin, inclusief de beruchte whiskyfles aan het einde.

Lydia, inmiddels allang geen huisgenootjes meer, en nu ook geen stadsgenootjes meer. Maar als ik je weer zie kletsen we gewoon weer verder.

Linda en Mariette, na de Corona toestand moeten we echt een vakantie in Andalusië plannen!

Judith, via Mom in Balance bleken we dezelfde passie voor hardlopen te delen, en het is ook prachtig om te zien hoe onze kinderen samen spelen en de wereld ontdekken.

Lieve Iris, Lilian, Annikki en Pip, bedankt voor alle broodnodige afleiding. Gelukkig is Haarlem om de hoek en lukt het nog regelmatig om spontane borrels/etentjes in te plannen.

Lieve schoonfamilie (Marelva, Gilbert, Yuli en Luis), dank jullie wel voor jullie interesse en steun en natuurlijk ook voor alle oppasuurtjes.

Jessica en Chris, wat toevallig allebei tegelijk een eeneiige tweeling, superfijn om met jullie dit avontuur te delen.

Lieve Eva, jij bent een aanwinst voor onze familie, op naar een mooie toekomst samen!

Lieve Sander en Wellington, door dezelfde combi van business en medisch is het altijd vruchtbaar om met jullie te sparren over onze en jullie toekomstplannen. Nu jullie nieuwe huis en mijn proefschrift eindelijk af zijn, komen we vaker richting het 'Grunnens Laand' om van jullie kookkunsten en rust daar te genieten.

Lieve pap en mam, dank voor jullie onvoorwaardelijke liefde. Mijn onbezorgde jeugd heeft gezorgd dat ik nu ben wie ik ben. Jullie steun was de afgelopen jaren onmisbaar, bedankt voor alle op en neertjes Assen – Amsterdam.

Lindo, mijn allerliefste, samen staan we sterk. Door jou positieve en opportunistische levensstijl denk jij altijd in mogelijkheden. Met Norah en Elaine is ons gezin compleet en genieten we van alle mooie momenten en avonturen in het leven.

Curriculum Vitae

Margriet Kwint werd op 14 december 1981 geboren in Assen. In 2000 haalde zij haar vwo-diploma aan het Dr. Nassau college te Assen. Daarna deed zij de studie HBO-Medisch Beeldvormende en Radiotherapeutische Technieken aan de Hanzehogeschool in Groningen. Vervolgens werkte zij 3 jaar als radiotherapeutisch laborant in het Antoni van Leeuwenhoek in Amsterdam. In 2007 startte zij met de opleiding als Physician Assistant aan de InHolland Graduate School in Amsterdam en werkte als Physician Assistant in opleiding op de afdeling radiotherapie in het Antoni van Leeuwenhoek. Tijdens het afstudeeronderzoek voor deze opleiding werd haar interesse voor onderzoek gewekt. In 2010 studeerde zij af als Physician Assistant en daarna bleef zij werken als Physician Assistant op de afdeling radiotherapie in het Antoni van Leeuwenhoek met als aandachtsgebied radiotherapie bij longkanker. In 2017 startte zij officieel een promotieonderzoek, onder leiding van prof. M.M. Verheij, prof.dr.ir. J.J. Sonke, Dr. J.S.A. Belderbos en Dr. I. Walraven. Dit promotieonderzoek werd gecombineerd met haar werk in de patiënten zorg. Margriet is getrouwd met Lindomar Minguel en is de trotse moeder van tweeling Norah en Elaine.

PhD portfolio

Graduate school Oncology Amsterdam (OOA)

Department:	Radiation Oncology
Institute:	Antoni van Leeuwenhoek hospital
PhD student:	Margriet Henrianne Kwint
PhD period:	2017-2020
PhD supervisors:	Prof. Dr. M. Verheij
	Prof. Dr. Ir. J.-J. Sonke
	Dr. J.S.A. Belderbos
	Dr. I. Walraven

Supervising committee of the graduate school Amsterdam

Prof. Dr. M. Hauptmann

Dr. A.J. Langen

Name activities	**Year**	**EC**
Courses and workshops		
Research integrity Course AUMC	2020	2
Scientific integrity course OOA	2018	0.5
Joint Modelling in R - Erasmus Summer School	2018	1,5
PhD annual graduate retreat OOA	2018	2
Good Clinical Practice course	2018	0,5
Latent Class Mixed and Joint modelling in R - ESTRO travel grand, University of Bordeaux	2017	1,5
English writing and Presenting in Biomedicine course OOA	2015	1,5
Basic Medical Statistics OOA	2014	1,5
Basic Clinical Radiobiology course ESTRO	2012	1,5
Basis cursus Oncologie NVRO	2011	2
Conferences + presentations		Max of 4 EC points
SASRO, Zurich - Switserland (Oral)	2018	
WCLC, Yokohama - Japan (Poster)	2017	
ISRS, Montreux - Switserland (Oral)	2017	
ESTRO, Turin - Italy (Poster)	2016	
WCLC, Denver - USA (Oral)	2015	
WCLC, Sydney - Australia (Oral)	2013	
ESMO Geneva- Switserland (Oral)	2011	

Name activities	Year	EC
WCLC, Amsterdam - Netherlands (Oral)	2011	
Other		
Teaching e.g. lecturing and supervision of interships	2010-2020	6
Member of Members council NAPA	2016-2020	2
Department Journal club meetings	2017-2020	3
Participation in department research group	2017-2020	3
IKNL meetings	2017-2020	1
Total		**33.5**