Innovations in the treatment of non-small cell lung cancer

Citation for published version (APA):

Wink, K. C. J. (2019). *Innovations in the treatment of non-small cell lung cancer*. [Doctoral Thesis, Maastricht University]. Optima Grafische Communicatie. <https://doi.org/10.26481/dis.20191204cw>

Document status and date:

Published: 01/01/2019

DOI:

[10.26481/dis.20191204cw](https://doi.org/10.26481/dis.20191204cw)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Innovations in the treatment of non-small cell lung cancer

Krista Christina Johanna Wink

© Krista Wink, Maastricht 2019

Cover design: Lars van Doorn

Lay-out and printing: Optima Grafische Communicatie

ISBN: 978-94-6361-351-4

Innovations in the treatment of non-small cell lung cancer

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, prof. dr. Rianne. M. Letschert,
volgens het besluit van het College van Decanen
in het openbaar te verdedigen
op woensdag 4 december 2019 om 10.00 uur

door

Krista Christina Johanna Wink

Promotores

Prof. dr. D.K.M. de Ruyscher

Prof. dr. E.G.C. Troost (Technische Universität Dresden, Duitsland)

Copromotores

Dr. A.A.W. van Baardwijk

Beoordelingscommissie:

Prof. dr. A.M.C. Dingemans (voorzitter)

Prof. dr. L.J. Boersma

Prof. dr. P.E. Postmus (Leids Universitair Medisch Centrum)

Dr. ir. A.C. Knopf (Universitair Medisch Centrum Groningen)

Voor oma

CONTENTS

Chapter 1	Introduction and outline	9
Chapter 2	Nodal recurrence after stereotactic ablative radiotherapy for early stage non-small cell lung cancer: incidence and proposed risk factors	27
Chapter 3	Contact of a tumour with the pleura is not associated with regional recurrence following stereotactic ablative radiotherapy for early stage non-small cell lung cancer	51
Chapter 4	Improved progression free survival for diabetic patients with locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy	85
Chapter 5	Particle therapy for non-small cell lung tumours: where do we stand? A systematic review of the literature	85
Chapter 6	Photons, protons or carbon ions for stage I non-small cell lung cancer? Results of the multicentric ROCOCO <i>in silico</i> study	113
Chapter 7	Photons or protons for re-irradiation in (non-)small cell lung cancer? Results of the multicentric ROCOCO <i>in silico</i> study	135
Chapter 8	General discussion and future perspectives	151
Chapter 9	Valorisation	169
	Samenvatting	175
	Dankwoord	183
	Curriculum Vitae	191
	Publications and grants	195

CHAPTER 1

Introduction and outline

GENERAL INTRODUCTION

Lung cancer is the leading cause of cancer death in both men and women, accounting for almost 20% of all cancer-related deaths. The world age-adjusted incidence rates of lung cancer for men and women were 34.2 and 13.6 per 100.000 in 2012, respectively, translating into 1.8 million new cases of lung cancer that year ¹. The median age at diagnosis is 70 years ². Even though most lung cancers can be attributed to smoking, it is estimated that 25% of all lung cancers is not related to tobacco use (15% in men and 53% in women)³. Approximately 83% of all lung cancers consist of non-small cell lung cancers (NSCLC) and 13% are small cell lung cancers (SCLC) ². Most patients are diagnosed at an advanced disease stage, most likely due to the lack of symptoms in earlier stages ². In 2015, 51% of all NSCLC patients had stage IV disease at diagnosis, versus 23% stage III, 10% stage II and 16% stage I ⁴.

Over the last 20 years, the survival of lung cancer has increased across all disease stages ^{5,6}. This is the likely result of improvements in surgical techniques and perioperative care, the introduction of modern three-dimensional conformal radiation therapy (3D-CRT) techniques and an increased proportion of patients receiving concurrent or sequential chemoradiation or palliative systemic therapy ^{5,7,8}. Notably, a part of the improvement in prognosis can also be explained by the increased use of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) for staging, which could have led to stage migration and an apparent improvement in survival (the so-called 'Will Rogers phenomenon') ^{6,9}. Despite all the progress that was made, the overall prognosis of lung cancer remains poor ². The 5-year overall survival (OS) rates of NSCLC are approximately 70-80% for stage I disease, 50% for stage II disease, 20-40% for stage III disease and 6% for Stage IV ¹⁰.

Treatment of early stage non-small cell lung cancer

For the majority of patients with stage I or II NSCLC, the mainstay of treatment is surgery, with 69% of patients undergoing an operation (usually a lobectomy with systematic lymph node dissection) ^{2,11}. For patients with irresectable disease, inoperable patients or patients unwilling to undergo surgery, radiotherapy is a widely accepted alternative ¹¹. Approximately 15% of early stage lung cancer is treated with radiotherapy alone ². In early stage disease, curative radiotherapy can consist of stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT) ¹¹. SABR is a highly accurate technique for delivering external beam radiation therapy to a pulmonary tumour in typically 3-8 fractions, using high doses of irradiation and steep dose gradients ¹². A 4-dimensional computed tomography scan (4D-CT) visualizing the tumour position in all breathing phases is used for SABR planning to account for tumour motion. Because of highly precise set-up verification protocols (3D or 4D cone beam CTs) and highly

conformal treatment planning with state of the art intensity modulated radiotherapy beams or dynamic arcs, small margins can be applied. Even patients with significant (pulmonary) comorbidities or low performance index can receive SABR. The introduction of SABR has led to less untreated patients and an improved OS rate in patients 75 years of age or older ¹³. If SABR is deemed too risky, for example in tumours adjacent to the oesophagus or proximal bronchial tree, radiotherapy should preferably be accelerated or hypofractionated (fraction size >2Gy) to reduce overall treatment time and improve treatment efficacy ^{14,15}.

For both lobectomy and SABR, reported 5-year local control rates are approximately 90% ¹⁶⁻¹⁸. In selected cases, adjuvant systemic therapy following surgery can be beneficial. For example, in patients with (unexpected) pN1 (involved ipsilateral peribronchial and/or hilar and/or intrapulmonary lymph nodes) or pN2 disease (involved ipsilateral subcarinal and/or mediastinal lymph nodes), an absolute improvement in overall survival of 4-5% was found at 5 years following adjuvant platinum-based chemotherapy ¹⁹. Adjuvant systemic treatment can also be considered in larger tumours measuring more than 4 cm ¹¹. However, adjuvant chemotherapy is rarely given after SABR. As more younger and operable, otherwise healthy patients are receiving SABR, trials on the role of adjuvant treatment in this setting are warranted ^{20,21}. Postoperative radiotherapy is indicated in case of a microscopic or macroscopic positive resection margin (R1 or R2 resection, respectively) and is considered in case of unexpected pN2 lymph nodes ^{11,22,23}.

Treatment of locally advanced non-small cell lung cancer

Locally advanced disease (stage IIIA and IIIB) is typically treated with a combination of definitive cisplatinum-based chemotherapy and radiotherapy up to a dose of 60-66Gy, using state of the art radiotherapy with PET-based planning and intensity modulated beams or dynamic arcs (please refer to paragraph 'developments in radiotherapy for (lung) cancer' for more detailed information on planning techniques) ^{11,24}. Preferably, chemotherapy and radiotherapy are administered concurrently, with the first fraction of radiotherapy administered at the first or second course of chemotherapy. Concurrent chemoradiotherapy results in an absolute improvement of overall survival of 4.5% at 5 years compared to the sequential approach, although at the cost of increased acute grade 3-4 oesophageal toxicity (increased from 4% to 18%) ²⁵. In case of a large tumour volume resulting in exceedance of radiation dose constraints and/or a patient in marginal condition, a sequential treatment is preferred ¹¹. Surgery is not typically recommended for patients with stage IIIB or IIIC disease (N3 nodal involvement (supraclavicular or contralateral lymph nodes) or cT3N2 or cT4N2 disease). However, there can be a role for surgery in stage IIIA NSCLC. Generally, patients with large tumours without mediastinal involvement (cT3N1, cT4N0, cT4N1) can be treated with upfront surgery

followed by adjuvant chemotherapy ^{11,26}. For patients with smaller cT1 and cT2 tumours and single-station N2 mediastinal disease (based on clinical staging and confirmed with biopsy), a primary resection can be followed by adjuvant chemotherapy or induction chemo(radio)therapy can be followed by a resection ^{11,26-29}. In these complex, multimodality treatment strategies, careful case discussions in an experienced multidisciplinary tumour board are essential. For potentially resectable superior sulcus tumours, concurrent chemoradiotherapy followed by a resection is the preferred treatment ¹¹.

Unfortunately, despite the multimodality approach, survival of locally advanced NSCLC remains poor due to frequent local and distant relapse. In the field of radiotherapy, attempts have been made to improve prognosis by shortening overall treatment time (acceleration), increasing total dose (dose-escalation) and/or the development of advanced radiotherapy techniques ³⁰. The effect of modified radiotherapy in the form of acceleration and/or hyperfractionation (decreasing the dose per fraction, but administering two or three fractions per day) on prognosis was summarised in a meta-analysis by Mauguen *et al* ¹⁴. Compared to conventional radiotherapy, modified radiotherapy resulted in an absolute 2.5% improvement in 5-year OS of non-metastatic NSCLC ¹⁴.

The benefit of dose-escalation was investigated in the RTOG 0617 study. A standard dose arm (60Gy in 30 fractions) was compared with a high dose arm (74Gy in 37 fractions). Patients in both arms received concurrent chemotherapy consisting of weekly paclitaxel/carboplatin with or without cetuximab. Unexpectedly, overall survival was worse in the high dose arm (median OS 29 months *versus* 20 months) ³¹. The results of another dose-escalation study, the PET-boost trial (NCT01024829), are upcoming and may provide further clarification in the dose-escalation matter. In this phase 2 trial, the benefit of maximum dose escalation to A) the entire primary tumour and B) to the region with the highest FDG uptake is investigated ³². Although the incidence of brain metastasis in stage III NSCLC is high (approximately 30% at 2 years), prophylactic cranial irradiation (PCI) is not a standard part of the treatment. PCI has been shown to reduce the incidence of symptomatic brain metastasis without a significant improvement in OS, while increasing the risk of neurocognitive decline ³³. The systemic treatment of locally advanced NSCLC is also evolving, with numerous trials enrolling patients for studies adding systemic therapy in (neo)adjuvant setting. For example, there are high expectations for adjuvant immune checkpoint inhibitor immunotherapy, e.g. the inhibition of programmed cell death-1 (PD-1) receptor or its ligand PD-L1 in stages I-III NSCLC ^{11,34}. In the adjuvant setting, the administration of Durvalumab (a PD-L1 inhibitor) has led to a significantly longer progression free survival and a 10% improvement in 2-year OS (66% *versus* 56%) ³⁵.

Treatment of recurrent NSCLC and stage IV non-small cell lung cancer

The 2-year rate of isolated (loco)regional failure following radical treatment NSCLC is approximately 5-10% for early stage NSCLC and 30-40% for locally advanced disease^{31,36,37}. The preferred treatment depends on the patient performance status, the extent and location of the disease recurrence and the previous treatment. Possibilities include definite surgery (+/- adjuvant systemic therapy), SABR, definite conventional re-irradiation (+/- concurrent chemotherapy) or palliative re-irradiation or systemic therapy. Re-irradiation of recurrent lung cancer can be very challenging and harbours a risk of serious treatment-related toxicity due to normal tissue damage, especially when re-irradiating critical mediastinal structures (e.g. large vessels, trachea, bronchi, oesophagus)^{38,39}.

The majority of patients with NSCLC eventually develop distant metastases, either at diagnosis or following curative (re-)treatment. There are many types of systemic agents available in case of stage IV disease in patients fit enough to undergo systemic treatment. A pathological diagnosis including molecular testing on epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene receptor tyrosine kinase (ROS1) and PD-1/PD-L1 testing is required. The preferred option depends on the type of tumour (squamous *versus* non-squamous), EGFR/ALK/ROS1 mutation profile and level of PD-1/PD-L1 expression⁴⁰. In case a patient is unfit for systemic therapy and/or has a symptomatic metastatic lesion, palliative radiotherapy can be given. Symptomatic brain metastases can be treated with radiosurgery (generally up to 4 metastases) or whole brain radiotherapy (WBRT), provided patients have a good performance and a reasonable prognosis⁴¹. Still, survival after WBRT for lung cancer is poor (median 2.7 months) and a more restrictive use of WBRT may be appropriate, especially in the elderly^{42,43}.

Developments in radiotherapy for (lung) cancer

As previously described, radiation therapy is often an integral part of lung cancer treatment and is most often delivered using photons (X-rays) produced at linear accelerators (linacs). In ionising radiation with photons, tissue interactions occur throughout the course of the beam path, inducing damage to the genetic material (DNA) of the encountered cells. As a result of this damage, tumour cells are killed or stop dividing. Both normal cells and cancer cells are damaged by radiation, but normal cells have a better repair mechanism and thus usually recover from the damaging effects of radiation. However, the effects of the radiation on normal cells can lead to significant and invalidating side effects, both during the course of the treatment (acute toxicity, e.g. esophagitis, coughing, dyspnoea) or in the long term (late toxicity, e.g. fibrosis or radiation pneumonitis).

Over the last three decades, photon irradiation for (lung) cancer has evolved from conventional radiotherapy fields (forward planned 3D-CRT) to inversely planned intensity

modulated radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), allowing for beam modulation during treatment (Figure 1)⁸. Furthermore, image guided and adaptive radiotherapy have become the standard of care in most Dutch departments for Radiation Oncology. This modernisation of radiotherapy techniques has increased target conformity thereby reducing doses to organs at risk (OAR) and, consequently, reducing treatment toxicity, while improving disease outcome^{8,44,45}.

Worldwide, an increasing number of patients is being treated with charged particles instead of photons, namely protons and heavy ions (typically carbon ions)⁴⁷. At present, three proton therapy centres have started clinical operation in the Netherlands. In ionising radiation with photons, dose deposition is higher closer to the beam entry point and decreases with depth, with a considerable exit dose. Conversely, in proton and carbon-ion therapy, the deposited dose increases slowly with depth and close to the end of the particles' range, a narrow maximum peak of dose deposition occurs, the so-called Bragg peak (Figure 2). This Bragg peak is a unique characteristic of particle therapy. The depth of the Bragg peak depends on the particles' initial energy and encountered tissue density. Distal to the Bragg peak, a rapid dose falloff is achieved, resulting in a lack of exit dose. To ensure sufficient tumour coverage, the Bragg peak needs to be widened to achieve a spread-out Bragg peak (SOBP, Figure 2). The Bragg peak is the most important physical advantage of particles over photons, as the dose to surrounding healthy tissues will be lower with particles. Consequently, treatment toxicity may be reduced because organs at

Figure 1: Dose distribution (% of the prescribed dose) using different radiotherapy delivery techniques in a patient with oesophageal cancer. The dose to the planning target volume (PTV) is most conformal in the modulated arc plan as less dose is deposited in healthy surrounding tissues. Abbreviations: 3D-RT= three-dimensional conformal radiation therapy, s-IMRT = static intensity modulated radiation therapy, mARC = modulated arc (figure adopted from Choi et al.⁴⁶).

Figure 2: A comparison of the depth profiles of an X-ray (photon) beam (red line) and proton beams with their individual Bragg peaks (blue lines). The sum of the individual Bragg peaks forms the spread-out Bragg peak (SOBP, dashed blue line) covering the tumour. The pink area represents the 'excess' dose deposited from photons to the shallow and deep healthy tissues (figure was adopted from Wikipedia).

risk surrounding the tumour can be spared. Furthermore, dose escalation at identical normal tissue toxicity can be attempted, possibly improving local tumour control.

In the early years of particle therapy, passively scattered proton or carbon-ion beams were employed to form a SOBP. In the passive scattering technique, a monoenergetic beam is spread by scattering material in the path of the particles. A collimator and a compensator are needed to conform the dose to the target volume (Figure 3A). The more recent particle therapy centres generally opted for pencil-beam scanning (PBS), also called active scanning or spot scanning, enabling intensity-modulated proton or carbon-ion therapy (IMPT or IMIT, respectively) ⁴⁷. In PBS, a tumour is irradiated using a narrow ('pencil') particle beam that is magnetically scanned across the target volume. By changing the beam energy, the pencil beams can be placed at different depths within the target. As a result, highly conformal particle therapy plans can be created (Figure 3B). A downside of PBS is the fact that the irradiation of moving tumours (as is often the case in lung cancer) is more complex compared with passive scattering. Motion management techniques such as gating, tracking and rescanning are essential to ensure target coverage ^{47,48}.

PURPOSE AND OUTLINE

As previously described, the overall outcome of non-small cell lung cancer remains poor despite the implementation of advanced radiation treatment and delivery techniques

Figure 3: A) passive scattering and B) pencil beam scanning (figure adopted from Son et al ⁴⁹).

and the administration of (concurrent) systemic therapy. Even though the aforementioned developments have led to some improvement, the absolute gain in overall survival and tumour control has been modest. Furthermore, especially in locally advanced NSCLC, the toxicity associated with the combined treatment modality is considerable. Also, possibilities for re-irradiation can be limited in previously irradiated lung cancer when the maximum tolerable dose to organs at risk has been reached. Therefore, there is a need for investigation of innovative strategies to optimise the treatment and thus outcome of non-small cell lung cancer, without increasing treatment toxicity. This was the main purpose of the current thesis.

With regard to this main purpose, the following topics are addressed:

- Lymph node recurrence following SABR for early stage NSCLC
- Metformin use during concurrent chemoradiotherapy for locally advanced NSCLC
- Particle therapy for early stage and recurrent NSCLC

Lymph node recurrence following SABR for early stage NSCLC

Following surgery for early stage, clinically node negative NSCLC, patients with unexpected (occult) involvement of dissected regional lymph nodes are known to be at risk for lymph node recurrence and have a worse outcome ^{50,51}. Therefore, adjuvant systemic therapy and/or adjuvant radiotherapy is often considered in these patients ^{11,22}. In SABR, regional lymph nodes are not surgically removed and thus left untreated except for the

incidental dose to the lymph nodes in the beam path. Not knowing the pathological regional lymph node status in SABR means prognostic information is lacking. Therefore, we felt it was necessary to identify other risk factors for (regional) recurrence to guide diagnostic and adjuvant treatment strategies. This is especially relevant as more younger and otherwise healthy patients are receiving SABR: they are potentially more likely to tolerate and benefit from adjuvant systemic therapy compared to the typical elderly and frail patients who have received SABR in the past. An important risk factor known from the surgical literature is visceral pleural invasion (VPI). When present, it has been shown to result in a worse outcome with respect to locoregional control and survival in surgical patients⁵²⁻⁵⁶. Its prognostic value for patients treated with SABR is unclear. We formulated the following hypothesis for the SABR population:

‘Visceral pleural invasion is a risk factor for regional recurrence following SABR’.

To be able to test this hypothesis, we started by performing a systematic review of the literature on the incidence of lymph node recurrence in patients who have received SABR for early stage NSCLC. The literature was also searched for possible risk factors (including VPI) for lymph node recurrence following SABR or surgery. The results of this systematic review are reported in **chapter 2**⁵⁷. To investigate the incidence of lymph node recurrence and predictive value of VPI in our own treatment population, we performed a retrospective cohort study on 574 patients from three institutions (MAASTRO clinic in Maastricht, Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital in Amsterdam and the University Hospital Carl Gustav Carus in Dresden). The effect of visceral pleural invasion was estimated using the planning CTs used for SABR planning. The results of this international study are reported in **chapter 3**.

Metformin use during concurrent chemoradiotherapy for locally advanced NSCLC

Even though the concomitant administration of chemotherapy and radiotherapy has improved survival in locally advanced NSCLC (6% at three years for concurrent versus sequential treatment), it has come at the cost of increased oesophageal toxicity²⁵. As previously described, the shortening of overall treatment time and dose escalation have also not led to the desired significantly improved outcome for patients with locally advanced NSCLC. Therefore, other strategies should be explored. An example is the repurposing of medication used for other diseases when they show anti-cancer properties *in vitro* and *in vivo*. Metformin is a well-known medicine used for type II diabetes that has also shown an anti-cancer effect in multiple pre-clinical and clinical studies^{58,59}. Several prospective and randomised trials have been completed or are ongoing, investigating its efficacy in NSCLC and other cancer types⁶⁰. We were interested in the prognostic effect of the use

of metformin during concurrent chemoradiotherapy in NSCLC. Our research was driven by the following hypothesis:

‘The use of metformin during concurrent chemoradiotherapy for locally advanced NSCLC can improve treatment outcome’

We performed a multi-institutional retrospective cohort study on 682 patients (59 metformin users and 623 control patients) who were treated for locally advanced NSCLC in one of three Dutch radiotherapy centres. We were able to report an improved progression free survival and distant metastasis free survival for diabetic patients with locally advanced NSCLC using metformin during their concurrent treatment ⁶¹. The results of this study are outlined in **chapter 4**.

Particle therapy for early stage and recurrent NSCLC

The favourable physical properties of particles make them appealing for the treatment of cancer, because it is possible to reduce the dose to the organs at risk and thereby possibly reduce treatment toxicity and/or enable isotoxic dose escalation. We were interested in the possibilities of this new and upcoming modality for the treatment of early stage and recurrent non-small cell lung cancer. The following hypotheses were formulated:

‘Stereotactic particle radiotherapy for early stage NSCLC can significantly decrease the dose to organs at risk, reduce the risk of treatment toxicity and enable isotoxic dose escalation’;

and

‘Particle therapy for recurrent NSCLC can significantly decrease the dose to surrounding (previously irradiated) healthy tissue, enabling re-irradiation to a higher dose than what would be possible with photon therapy’.

In **chapter 5**, the use of particle therapy (both protons and carbon-ions) is reviewed, including the worldwide clinical results published at that time ⁶². The reported tumour control and overall survival rates are comparable to those achieved with the traditional photon techniques. Still, a lot of challenges are present when irradiating moving lung tumours with particles. The effect of range uncertainties and interplay between protons and the moving target can influence the robustness of a treatment plan. The effects and uncertainties that need to be taken into account are discussed, as well as the possible methods to enhance robustness. To shed more light on the possibilities of particle therapy

in early stage lung cancer, an international *in silico* planning study was conducted within the Radiation Oncology COllaborative Comparison (ROCOCO) consortium⁶³. For each of 24 patients, a treatment plan was calculated with five different modalities: 3D-CRT, IMRT, VMAT, IMIT and double scattered proton therapy (DSP). The results in **chapter 6** show that peripherally located stage I NSCLC may not be the most relevant indication for proton therapy or carbon-ion therapy. Another *in silico* planning study was performed in the ROCOCO consortium on the possible benefits of particle therapy for re-irradiation of recurrent NSCLC. A comparison was made for seven modalities: VMAT, 3D-CRT, IMRT, Tomotherapy, CyberKnife, DSP and IMPT. The results are reported in **chapter 7**.

REFERENCES

1. Cheng TY, Cramb SM, Baade PD, Youlten DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(10):1653-1671.
2. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA: a cancer journal for clinicians*. 2016;66(4):271-289.
3. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers--a different disease. *Nature reviews Cancer*. 2007;7(10):778-790.
4. Overlevingscijfers niet-kleincellige longkanker. Integraal Kankercentrum Nederland (IKNL). <https://www.kanker.nl/bibliotheek/niet-kleincellige-longkanker/wat-is/1618-overlevingscijfers-niet-kleincellige-longkanker>. Published 2015. Updated August 2018.
5. 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(2):291-298.
6. Driessen EJ, Aarts MJ, Bootsma GP, van Loon JG, Janssen-Heijnen ML. Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990-2014): Disparities between younger and older patients. *Lung Cancer*. 2017;108:198-204.
7. Abbas AE. Surgical Management of Lung Cancer: History, Evolution, and Modern Advances. *Curr Oncol Rep*. 2018;20(12):98.
8. Diwanji TP, Mohindra P, Vyfhuis M, et al. Advances in radiotherapy techniques and delivery for non-small cell lung cancer: benefits of intensity-modulated radiation therapy, proton therapy, and stereotactic body radiation therapy. *Translational lung cancer research*. 2017;6(2):131-147.
9. Morgensztern D, Goodgame B, Baggstrom MQ, Gao F, Govindan R. The effect of FDG-PET on the stage distribution of non-small cell lung cancer. *J Thorac Oncol*. 2008;3(2):135-139.
10. Goldstraw P, Chansky K, Crowley J, 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.
11. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(suppl_4):iv1-iv21.
12. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. *Journal of thoracic disease*. 2011;3(3):189-196.
13. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(35):5153-5159.
14. Mauguén A, Le Pechoux C, Saunders MJ, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(22):2788-2797.
15. Schneider BJ, Daly ME, Kennedy EB, Stiles BM. Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline Summary. *Journal of oncology practice*. 2018;14(3):180-186.

16. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637.
17. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2008;70(3):685-692.
18. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *International journal of radiation oncology, biology, physics*. 2012;83(1):348-353.
19. Artal Cortes A, Calera Urquiza L, Hernando Cubero J. Adjuvant chemotherapy in non-small cell lung cancer: state-of-the-art. *Translational lung cancer research*. 2015;4(2):191-197.
20. Jumeau R, Bahig H, Filion E, et al. Assessing the Need for Adjuvant Chemotherapy After Stereotactic Body Radiation Therapy in Early-stage Non-small Cell Lung Carcinoma. *Cureus*. 2016;8(11):e901.
21. Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2019;132:188-196.
22. Billiet C, Decaluwe H, Peeters S, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2014;110(1):3-8.
23. Billiet C, Peeters S, Decaluwe H, Vansteenkiste J, Mebis J, Ruysscher D. Postoperative radiotherapy for lung cancer: Is it worth the controversy? *Cancer treatment reviews*. 2016;51:10-18.
24. Grootjans W, de Geus-Oei LF, Troost EG, Visser EP, Oyen WJ, Bussink J. PET in the management of locally advanced and metastatic NSCLC. *Nature reviews Clinical oncology*. 2015;12(7):395-407.
25. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(13):2181-2190.
26. Bryan DS, Donington JS. The Role of Surgery in Management of Locally Advanced Non-Small Cell Lung Cancer. *Curr Treat Options Oncol*. 2019;20(4):27.
27. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*. 2009;374(9687):379-386.
28. Eberhardt WE, Pottgen C, Gauler TC, et al. Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPAUE). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(35):4194-4201.
29. Pless M, Stupp R, Ris HB, et al. Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial. *Lancet*. 2015;386(9998):1049-1056.
30. Christodoulou M, Bayman N, McCloskey P, Rowbottom C, Fivre-Finn C. New radiotherapy approaches in locally advanced non-small cell lung cancer. *European journal of cancer*. 2014;50(3):525-534.
31. Bradley JD, Paulus R, Komaki R, 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. *The Lancet Oncology*. 2015;16(2):187-199.

32. van Elmpt W, De Ruyscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;104(1):67-71.
33. De Ruyscher D, Dingemans AC, Praag J, et al. Prophylactic Cranial Irradiation Versus Observation in Radically Treated Stage III Non-Small-Cell Lung Cancer: A Randomized Phase III NVALT-11/DLCRG-02 Study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018;36(23):2366-2377.
34. Deslypere G, Gullentops D, Wauters E, Vansteenkiste J. Immunotherapy in non-metastatic non-small cell lung cancer: Can the benefits of stage IV therapy be translated into earlier stages? *Ther Adv Med Oncol*. 2018;10:1758835918772810.
35. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
36. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer*. 2017;123(16):3031-3039.
37. Ball D, Mai GT, Vinod S, et al. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *The Lancet Oncology*. 2019.
38. Vyfhuis MAL, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *Journal of thoracic disease*. 2018;10(Suppl 21):S2522-S2536.
39. De Ruyscher D, Faivre-Finn C, Le Pechoux C, Peeters S, Belderbos J. High-dose re-irradiation following radical radiotherapy for non-small-cell lung cancer. *The Lancet Oncology*. 2014;15(13):e620-624.
40. Hanna N, Johnson D, Temin S, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(30):3484-3515.
41. Andratschke N, Kraft J, Nieder C, et al. Optimal management of brain metastases in oncogenic-driven non-small cell lung cancer (NSCLC). *Lung cancer*. 2019;129:63-71.
42. Jeene PM, de Vries KC, van Nes JGH, et al. Survival after whole brain radiotherapy for brain metastases from lung cancer and breast cancer is poor in 6325 Dutch patients treated between 2000 and 2014. *Acta Oncol*. 2018;57(5):637-643.
43. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014.
44. Yom SS, Liao Z, Liu HH, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *International journal of radiation oncology, biology, physics*. 2007;68(1):94-102.
45. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol*. 2017;35(1):56-62.
46. Choi KH, Kim J, Lee SW, Kang YN, Jang H. Dosimetric comparison between modulated arc therapy and static intensity modulated radiotherapy in thoracic esophageal cancer: a single institutional experience. *Radiation oncology journal*. 2018;36(1):63-70.
47. Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. *Nat Rev Clin Oncol*. 2017;14(8):483-495.

48. Chang JY, Zhang X, Knopf A, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. *International journal of radiation oncology, biology, physics*. 2017;99(1):41-50.
49. Son J, Lee SB, Lim Y, et al. Development of Optical Fiber Based Measurement System for the Verification of Entrance Dose Map in Pencil Beam Scanning Proton Beam. *Sensors*. 2018;18(1).
50. Rusch VW, Hawes D, Decker PA, et al. Occult metastases in lymph nodes predict survival in resectable non-small-cell lung cancer: report of the ACOSOG Z0040 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(32):4313-4319.
51. Varlotto JM, Yao AN, DeCamp MM, et al. Nodal stage of surgically resected non-small cell lung cancer and its effect on recurrence patterns and overall survival. *International journal of radiation oncology, biology, physics*. 2015;91(4):765-773.
52. Jiang L, Liang W, Shen J, et al. The impact of visceral pleural invasion in node-negative non-small cell lung cancer: a systematic review and meta-analysis. *Chest*. 2015;148(4):903-911.
53. Kudo Y, Saji H, Shimada Y, et al. Impact of visceral pleural invasion on the survival of patients with non-small cell lung cancer. *Lung cancer*. 2012;78(2):153-160.
54. Inoue M, Minami M, Shiono H, Sawabata N, Ideguchi K, Okumura M. Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2 cm or less in diameter: pleural invasion and increase of serum carcinoembryonic antigen level as predictors of nodal involvement. *The Journal of thoracic and cardiovascular surgery*. 2006;131(5):988-993.
55. Yang X, Sun F, Chen L, et al. Prognostic value of visceral pleural invasion in non-small cell lung cancer: A propensity score matching study based on the SEER registry. *Journal of surgical oncology*. 2017;116(3):398-406.
56. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2005;130(1):160-165.
57. Wink KCJ, van Baardwijk A, Troost EGC, De Ruyscher D. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. *Cancer Treat Rev*. 2017;56:8-15.
58. Yousef M, Tsiani E. Metformin in Lung Cancer: Review of in Vitro and in Vivo Animal Studies. *Cancers*. 2017;9(5).
59. Tronccone M, Cargnelli SM, Villani LA, et al. Targeting metabolism and AMP-activated kinase with metformin to sensitize non-small cell lung cancer (NSCLC) to cytotoxic therapy: translational biology and rationale for current clinical trials. *Oncotarget*. 2017;8(34):57733-57754.
60. Chae YK, Arya A, Malecek MK, et al. Repurposing metformin for cancer treatment: current clinical studies. *Oncotarget*. 2016;7(26):40767-40780.
61. Wink KC, Belderbos JS, Dieleman EM, et al. Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy. *Radiother Oncol*. 2016;118(3):453-459.
62. Wink KC, Roelofs E, Solberg T, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol*. 2014;4:292.
63. Wink KCJ, Roelofs E, Simone CB, 2nd, et al. Photons, protons or carbon ions for stage I non-small cell lung cancer - Results of the multicentric ROCOCO in silico study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2018.

CHAPTER 2

Nodal recurrence after stereotactic ablative radiotherapy for early stage non-small cell lung cancer: incidence and proposed risk factors

Krista C.J. Wink, Angela van Baardwijk, Esther G.C. Troost, Dirk de Ruysscher

Cancer Treatment Reviews 2017; 56: 8-15

ABSTRACT

Stereotactic ablative radiotherapy (SABR) is an alternative to surgery for patients with early stage non-small cell lung cancer (NSCLC) who are inoperable due to comorbid disease or who refuse surgery. SABR results in an excellent local control rate of more than 90%, which is comparable to surgery, while short and long-term overall toxicity is low. Surgically treated patients are often more extensively staged pre-operatively, e.g. with endobronchial ultrasound and/or mediastinoscopy, and typically undergo intra-operative lymph node dissection or sampling. Occult nodal metastases (ONM), detected by lymph node dissection, have been shown to increase the incidence of regional recurrence (RR) after surgery, which is associated with poor outcome. In patients undergoing SABR, however, definite pathological nodal staging is lacking and so other ways to identify patients at high risk for ONM and RR are desirable.

The aim of this systematic review is to summarise the incidence of, and risk factors for, RR after SABR and compare these to those after surgery. The available evidence shows the incidence of RR after SABR or surgery to be comparable, despite more elaborate pre- and intra-operative lymph node evaluation in surgical patients. However, the fact that this finding is based on mostly retrospective studies in which the majority of patients treated with SABR were inoperable, needs to be taken into consideration. For now, there is no evidence that inoperable clinical stage I patients with no indication of pathological lymph nodes on PET/CT will benefit from more invasive lymph node staging prior to SABR.

BACKGROUND

The standard treatment option for patients with early stage non-small cell lung cancer (NSCLC) without lymph node involvement is a surgical tumour resection with a systematic hilar and mediastinal lymph node dissection (MLND). If patients are inoperable due to their age or comorbidities, or they refuse surgery, stereotactic ablative radiotherapy (SABR) is an alternative treatment option. SABR is the term describing the administration of high precision, high dose radiotherapy in a limited number of treatment fractions. Due to the high dose per fraction and the short overall treatment time, the radiobiological effectiveness of SABR is high (biologically effective dose [BED] >100Gy) resulting in excellent local control rates of over 90%, comparable to surgery^{1,2}. Unfortunately, no randomised trials on the outcome of SABR *versus* surgery in operable patients have been successfully conducted, most closing early due to poor accrual. However, a recently published pooled analysis of two of these randomised trials suggests an improved survival and better treatment tolerability for SABR compared to surgery¹. The overall toxicity is low and does not seem to adversely affect long-term lung functionality and quality of life, making it a suitable treatment option, especially for patients with a poor pulmonary function³⁻⁶.

Since the introduction of SABR more than a decade ago, the number of patients treated with this modality has increased over time⁷. Its use for early stage NSCLC has resulted in a decrease in the number of untreated elderly patients and an improved survival in this group⁸. An essential difference between stereotactic radiotherapy and surgery for early stage NSCLC is the evaluation of the regional lymph node stations. In patients who are fit enough to undergo a surgical resection, extensive preoperative staging of regional lymph nodes is performed⁹. If nodal involvement is diagnosed on ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), endobronchial ultrasound (EBUS), oesophageal ultrasound (EUS) and/or mediastinoscopy is subsequently performed. For medically inoperable patients undergoing SABR, staging is more often limited to an FDG-PET/CT scan, where small lymph node metastases are likely to be missed¹⁰⁻¹². Nevertheless, in cT1-2N0 patients, the probability of having mediastinal (N2) lymph node disease is only ~5%^{13,14}. Besides elaborate pre-operative staging, surgically treated patients routinely undergo either intra-operative lymph node sampling or a systematic hilar/mediastinal lymph node dissection. This procedure leads to nodal upstaging in 10-20% of the patients^{11,13,15}. Conversely, the regional lymph node stations of patients undergoing SABR are not sampled and left untreated, except for incidental dose to the lymph nodes close to the planning target volume (PTV) and/or in the beam path¹⁶.

Patients undergoing surgery who have (unexpected) regional lymph node involvement are known to have a worse prognosis, even when the involved nodes contain only microscopic disease¹⁷. Therefore, adjuvant chemotherapy and/or radiotherapy are considered in patients diagnosed with occult lymph node disease following surgery^{18,19}. The clinical relevance of not performing pathological lymph node staging for clinical stage I patients undergoing SABR is unclear. Does it result in more regional recurrences (RR) than in patients who had their lung tumour resected? Should more invasive staging prior to SABR be performed to diagnose nodal involvement?

The aim of the current systematic review is to shed more light on the outcome of SABR with respect to the regional lymph nodes. Studies on the incidence of, and risk factors for, regional failure following SABR will be discussed. These findings are compared to the incidence of RR after surgery and risk factors derived from surgical studies.

MATERIAL AND METHODS

Defining regional recurrence

To minimise heterogeneity in outcomes due to variable definitions of RR, only articles with a clear and comparable definition were included in this systematic review. The revised RECIST guideline (version 1.1) includes criteria for measuring pathological lymph nodes, whereas the original version does not²⁰⁻²². However, the assessment of lymph node recurrence in patients with previously clinically node negative disease (as is the case in the current review) remains somewhat unclear. The lack of a measurable lymph node of at least 1.5 cm at baseline means the 20% growth in diameter cannot be used to define progressive disease. According to RECIST, the growth of an existing lymph node to ≥ 1 cm in diameter or the occurrence of a 'new' lymph node ≥ 1 cm is pathological. However, we disagree that the diagnosis of a lymph node recurrence should be based solely on the diameter of a regional lymph node on CT. In clinical practice, we always require more 'proof' of recurrence to avoid unnecessary treatments with a risk of toxicity. For the purpose of the current review, we achieved group consensus on how to define RR during follow-up for patients who were clinically node negative before SABR. We agreed upon the following criteria: 1) a new or growing lymph node on CT combined with FDG-PET avidity, and/or 2) biopsy confirmed regional recurrence, and/or 3) continuing lymph node enlargement on serial CT scans. Studies not meeting one of these three criteria were excluded.

Search strategy

The PubMed database was searched for relevant articles up to August 2016, using the following search terms: 'non-small cell', 'NSCLC', 'lung cancer', 'lung neoplasm', 'lung tumour', 'early stage', 'stage 1', 'stage 2', 'failure(s)', 'recurrence(s)', 'outcome(s)', 'follow-up', 'progression', 'stereotactic radiotherapy', 'SBRT', 'SABR', 'radiosurgery', 'regional', 'nodal', 'mediastinal', 'lymph node(s)'. The literature search yielded 157 articles, which were all screened for eligibility by one of the authors (KW). Articles deemed relevant after title and abstract screening were selected for full text review (n=75). Both prospective and retrospective studies on the outcome of SABR in early stage (in)operable, clinically node negative, NSCLC patients treated with SABR were considered for inclusion. Studies comparing SABR with standard external beam radiation therapy (EBRT) or surgery were allowed, a minimal number of 20 treated patients was required and only studies published in English were included. In case of doubt about a study fulfilling the inclusion criteria, the study was read by all authors and group consensus was reached on inclusion.

Eventually, 13 of the 157 articles remained. The reference lists of included articles were searched for additional studies, resulting in another 3 included articles, leading to a total of 16 included articles (see Figure 1 for an overview of the search process and reasons for exclusion).

Figure 1: Flowchart outlining the search and research process. NSCLC = non-small cell lung cancer, RR = regional recurrence, SABR = stereotactic ablative radiotherapy.

Identical search terms were employed to identify risk factors for occult nodal metastases and nodal recurrences from the surgical literature (minus the radiotherapy terms), adding the following terms for further specification: 'resection', 'wedge', 'lobectomy', 'segmentectomy', 'surgery', '*NO' (* including variations), 'occult', 'sampling', 'dissection', 'prospective', 'clinical trial', 'retrospective', 'cohort'. Only studies meeting the earlier described criteria for defining regional recurrence were cited.

RESULTS

Study and patient characteristics

Table 1 summarises the results of the sixteen included studies. All studies were published between 2009 and 2016 and are mostly retrospective, evaluating between 20 and 483 patients. The median patient age ranged from 67 to 79 years and the median follow-up varied from 13 to 50 months. Most patients were treated for clinically node negative stage I and/or II NSCLC and were medically inoperable or they refused surgery. Some studies also included a small number of patients with M1 disease and/or synchronous lung tumours²³⁻²⁵. Patients with a diagnosis of recurrent lung cancer, previously treated with surgery or conventional radiotherapy, were occasionally included^{26,27}. It was decided not to exclude these studies, as these patients constituted only a small portion of the investigated cohorts. Patients were generally staged with at least a CT scan of chest and abdomen and/or FDG-PET/CT, and occasionally also underwent a mediastinoscopy, EBUS, and/or cerebral CT or magnetic resonance imaging (MRI) screening for brain metastases. A staging FDG-PET/CT was performed in 82-100% of the patients treated with SABR. Pathologic confirmation of the primary lung tumour was not necessarily required: biopsy proven NSCLC was present in 30 – 100% of the SABR cases.

Incidence of hilar/mediastinal lymph node metastases following SABR

The cumulative incidence of RR after SABR for early stage NSCLC varied from 0-28.6%, with a mean incidence of 9.6 % (Table 1). The addition of FDG-PET to a diagnostic chest CT enhanced the detection rate of RR after SABR²⁸. Most commonly, nodal recurrence was defined as an enlarged, FDG-avid lymph node on an FDG-PET/CT scan^{23-26,28-35}. One study required a biopsy to confirm recurrence³⁶. Others pursued biopsy confirmation when recurrence was suspected on serial CT scans or FDG-PET/CT, unless clear metastatic disease was present or the patient was believed to be too frail to tolerate salvage or palliative treatment^{16,23,26-28,32,35}.

The study by Chang *et al.*¹ is the first and only report of a randomised comparison between SABR and surgery for operable stage I NSCLC. The authors have performed a pooled analysis of two randomised controlled trials (the STARS trial, [NCT00840749] and

the ROSEL trial, [NCT00687986]) that both closed early due to slow accrual. Even though the definitions of RR in both trials did not entirely meet our criteria, we decided to include the pooled analysis since it is the only randomised comparison published so far. The authors in the ROSEL trial did not specify 'radiological progression', while in the STARS trial, the enlargement of a lymph node >1.0cm in the short axis on CT seemed to be enough to define regional recurrence (additional investigations were done if the lymph node was equivocally enlarged though). A total of 58 patients were included, 31 of whom were randomised to SABR, and 27 to surgery. The frequency of local, regional or distant metastasis was similar between the treatment groups. Four of the 31 patients treated with SABR developed a RR (12.9%) versus one patient in the surgery group (3.7%), and at three years, 90% of the patients in the SABR cohort *versus* 96% in the surgery group were free from RR ($p=0.32$). Of course, when interpreting these results, the small number of events should be taken into account as the statistical power to detect a significant difference is low.

Three additional studies compared the outcome of SABR for early stage NSCLC with a cohort of surgically treated patients (wedge resection, pneumonectomy or (sub)lobar resection)^{26,31,32}. Crabtree and colleagues³¹ compared outcomes of SABR and surgery in an unmatched cohort and in two separate propensity-matched analyses. The cumulative incidence of RR after SABR was 10%. Regional recurrence free survival was comparable (87% for SABR *versus* 95% for surgery at 3 years; $p=0.18$) in the final propensity-matched comparison of 56 patients matched on age, tumour size, comorbidity score, forced expiratory volume in the first second of expiration and tumour location. Overall survival (OS) seemed to be better for the surgical patients: the authors report a 3-year OS of 52% for SABR *versus* 68% for surgery ($p=0.05$)³¹. Another study reported on the outcomes of SABR or wedge resection for stage I NSCLC in patients ineligible for anatomic lobectomy³². A mediastinoscopy or lymph node dissection or both was performed in 71% of the patients undergoing surgery. The RR rate 2.5 years after SABR was 4% as opposed to 18% after wedge resection ($p=0.34$). After the exclusion of all cases of pathologic T4 disease, presumed synchronous primary tumours, and non-biopsied tumours, a statistical trend for RR was seen in favour of SABR (0% *versus* 18% at 2.5 years; $p=0.07$). Robinson *et al.*²⁶ investigated failure patterns after SABR or lobar resection (lobectomy or pneumonectomy) for pathologically confirmed clinical stage I NSCLC patients. Occult nodal involvement was discovered in 21.5% of the surgically treated group. Nodal control rates were similar for lobar resection and SABR (4-year-nodal control 82.9% *versus* 78.1%, $p=0.912$).

Badiyan *et al.*²⁹ reported on the patterns of failure and survival of bronchioloalveolar carcinoma (BAC, now called in situ pulmonary adenocarcinoma (AIS)) *versus* other early stage NSCLC patients. The authors concluded that BAC appears to have outcomes similar to other NSCLC subtypes, including the rate of RR (12% *versus* 20% at 3 years, $p=0.45$).

Table 1: study characteristics, regional recurrence rates and reported risk factors for nodal failure.

Name of first author	Study design	Patients (n)	Age (median)	FU (median, months)	% staging PETCT	Prescribed dose/n fractions	Treatment volume	Nodal failure / control	Risk factors
Badiyan ²⁹	Retrospective	5 BAC, 115 non-BAC	74	29 (39 for survivors)	93%	45-69Gy/ 3-6	ITV = MIP. Additional PTV expansion following RTOG guidelines.	3yr 12% BAC, 20% non-BAC (NS)	n/a
Bollineni ³⁰	Retrospective	132	75	17	100%	60Gy/3-8	n/a	MF 11.4%, 2yr MF 19% high SUV _{max} 12% low SUV _{max} (NS)	None found (multiple tested)
Bradley ²⁵	Prospective/ retrospective	91	71	18	100%	30-60Gy/3-5	ITV (= CTV) + 10mm CC and 5mm axial = PTV	7.7%	MVA: lower total Rx dose
Chang ¹	Pooled analysis of two randomised trials	31 SABR 27 surgery	67 (SABR) 67 (surgery)	40 (SABR) 35 (surgery)	100%	50-60Gy/3-5	STARS: GTV + 3mm = PTV. ROSEL: ITV + 3-5mm = PTV	12.9% (SABR), 3.7% (surgery) NC 3 yrs: 90% (SABR) vs 96% (surgery) (NS)	n/a
Collins ³⁶	Prospective	20	74	25 (survivors)	100%	42-60Gy/3	GTV + 5mm = PTV	0%	n/a
Crabtree ³¹	Retrospective	151 SABR, 458 surgery	74 (SABR), 66 (surgery) (5)	23 (SABR), 34 (surgery)	100%	45-60Gy/3-6	ITV (= CTV) + 10mm CC and 5mm axial = PTV	10% NC 1yr (SABR): 93%, 3yr 86%, 5yr 86%. Two matched cohorts (surgery vs SABR): NS	n/a
Ebright ²⁸	Retrospective	35	n/a	12.8	100%	50-60Gy/3-5	GTV + ≥5mm = PTV	28.6% (PET/CT, 60% biopsy confirmation) NC 2yr 52.1%	n/a

Table 1: study characteristics, regional recurrence rates and reported risk factors for nodal failure. (continued)

Name of first author	Study design	Patients (n)	Age (median)	FU (median, months)	% staging PETCT	Prescribed dose/ n fractions	Treatment volume	Nodal failure / control	Risk factors
Grills²²	Prospective/retrospective	55 SABR, 69 wedge resection,	78 (SABR), 74 (wedge) (5)	30	100%	48-60Gy/4-5	ITV + 4mm = CTV, CTV + ≥5mm = PTV	2.5yr 4%. Exclusion pT4, synchronous primary and no biopsy: statistical trend NF 2.5yrs: SABR 0% vs wedge resection 18% (NS)	n/a (not enough events)
Grills²³	Prospective/retrospective	483	74	19	88%	18-64Gy/1-15	different between centers	7.7% 2yr 11%, 3yr 14%	UVA: Synchronous primary tumors (MVA: NS), MVA: time PET to start SABR (NS trend) SUV _{max} not predictive
Horne³³	Retrospective	95	77	16	100%	60Gy/3	GTV + ≥5mm = PTV, additional margin based on motion for ITV	10.5% NC 2yr 90.5%	
Lao¹⁶	Retrospective case control study	19 cases, 38 matched controls	72 (cases), 75 (controls)	25.8 (cases), 28.8 (controls)	100% (cases) 82% (controls)	24-60Gy/1-10	CTV (= GTV + 0mm) fused = ITV, ITV + 5mm = PTV.	n/a	Lower mean ipsilateral hilar dose (cases 9.6Gy vs 22.4Gy for controls).
Nath²⁴	Retrospective	48 (50 lesions)	79	17 (21 for survivors)	94%	48-52Gy/4-5	ITV + 5mm = PTV (8mm CC if tumor in lower 2/3 of the lung)	6.5% 2yr 6%	None found (multiple tested)
Olsen³⁴	Prospective/retrospective	130	75	11 (9Gyx5), 16 (10Gyx5), 13 (18Gyx3)	97%	45-54Gy/3-5	ITV (= CTV) + 10mm CC and 5mm axial = PTV	11.5%	n/a

Table 1: study characteristics, regional recurrence rates and reported risk factors for nodal failure. (continued)

Name of first author	Study design	Patients (n)	Age (median)	FU (median, months)	% staging PETCT	Prescribed dose/n fractions	Treatment volume	Nodal failure / control	Risk factors
Robinson ²⁶	Retrospective	78 SABR, 260 lobar resection	76 (SABR)	50.3 (SABR)	n/a	45-54Gy/3-5	ITV + 10mm CC and 5mm axial = PTV	NC 4yr 78.1% (SABR) vs 82.9% (surgery) (NS)	None found (multiple tested)
			66 (lobar resection) (5)	51.3 (surgery)					
Shaverdian ³⁵	Retrospective	147	76	28.9	n/a	50-54Gy/3-4	ITV + 3mm transverse and 6mm longitudinal = PTV	NC 3yr 87%	UVA/MVA: lower pretreatment Hb level (3yr RC 95% vs 75% when Hb ≥ 12.2g/dL)
Spratt ²⁷	Retrospective	366	77	23	100%	45-60Gy/3-5	ITV + 2 or 3mm = CTV, + 5mm = PTV	1yr 7.7%, 2yr 16.1%, 3yr 17.4%	UVA/MVA: male gender

BAC = Bronchioloalveolar Carcinoma, CC = craniocaudal, CTV = clinical target volume, GTV = gross tumor volume, ITV = internal target volume, MF = mediastinal failure, MIP = maximum intensity projection, MVA = multivariate analysis, n = number, n/a = not applicable, NC = nodal control, NR = nodal recurrence, NS = not significant, Rx = radiotherapy, PTV = planning target volume, S = statistically significant, SABR = stereotactic ablative therapy, SUVmax = maximum standard uptake value, UVA = univariate analysis.

Identification of risk factors for nodal recurrence after SABR

In a retrospective study, Bollineni *et al.*³⁰ investigated the prognostic value of the FDG-PET based maximum standardised uptake value (SUV_{max}) at 12 weeks post-SABR. Fifteen of the 132 included patients developed mediastinal failure (11.4%). Mediastinal failure rates did not significantly differ between the high and low post-SABR SUV_{max} groups using a SUV_{max} cutoff value of ≥ 5 (2-year mediastinal failure 19% *versus* 12%, $p=0.392$). The prognostic value of FDG uptake in the primary tumour of stage I NSCLC patients was also studied by Horne *et al.*³³ The authors concluded that pre-SABR SUV_{max} predicted for progression free survival when considered as a continuous variable in a multivariate analysis, but it did not predict for regional control ($p=0.131$). Similarly, a non-significant trend for RR was found by Grills *et al.*²³ for the elapsed time from diagnostic FDG-PET to the start of SABR.

Lao *et al.*¹⁶ performed a case control study to determine the difference in the incidental dose to the hilar and mediastinal lymph nodes for stage I NSCLC patients with and without RR after SABR (19 cases *versus* 38 matched controls). The authors discovered that the mean ipsilateral hilar dose was significantly lower for patients with a RR (9.6Gy *versus* 22.4Gy; $p=0.014$; BED using an α/β ratio of 10Gy). A retrospective study by Bradley *et al.*²⁵ described the patterns of failure in 91 early stage NSCLC patients treated with SABR with a follow-up period of at least 6 months. Seven patients (7.7%) developed a nodal failure, either isolated or combined with local or distant failure. In a multivariate analysis, a higher prescribed radiation dose to the tumour was associated with fewer nodal and distant failures. The authors did not propose hypotheses to explain this finding, but incidental dose to mediastinal lymph nodes as described by Lao *et al.*¹⁶ is a possibility.

Shaverdian *et al.*³⁵ evaluated the prognostic value of pre-treatment anaemia among 147 patients with early-stage NSCLC treated with SABR. A lower pre-treatment haemoglobin level (optimal cut-off value 12.2g/dL) significantly predicted for poor regional control, both continuously and categorically (area under the ROC curve of 0.70). Using this cut-off value, the 3-year regional control rate was 95% for patients with a higher pre-treatment haemoglobin level, *versus* 75% for patients with a lower haemoglobin level before SABR ($p=0.02$). Pre-treatment anaemia did not predict for local or distant control in multivariate analysis ($p=0.94$ and $p=0.52$, respectively).

To establish the optimal surveillance regimen for patients treated with SABR, Spratt *et al.*²⁷ described recurrence patterns for 366 patients with biopsy proven stage I NSCLC, treated with SABR. The authors report a 2-year nodal failure rate of 16.1%, and on uni- and multivariate analysis, male gender was found to be a statistically significant predictor for RR (HR 0.58, $p=0.045$). Other evaluated prognostic factors, including patient age,

performance status, smoking status, histologic tumour type, tumour size and radiation dose, were not predictive for RR.

Incidence of regional recurrence and risk factors derived from surgical studies

Local-regional failure (LRF) rates and the distribution of recurrences were reviewed by Saynak and colleagues³⁷ for 335 patients who had undergone an anatomic complete resection of their lung tumour (pathologic stage T1-4 N0-1). The hilar and mediastinal lymph nodes were surgically evaluated in 95% of the patients; preoperatively through mediastinoscopy and/or peroperatively through sampling or dissection. The 5-year LRF rate was 24%, after a median follow-up time of 18 months. Tumour size and lympho-vascular invasion were predictive for LRF and a trend for visceral pleural invasion was noted. Fifteen percent of all patients developed a RR in the mediastinum; 3% developed a hilar lymph node recurrence. The fact that nodal sampling or dissection was not done systematically (*e.g.*, only 0 to 1 mediastinal lymph node stations were sampled in 17% of the patients) did not appear to be relevant for the RR rate in this study, although no formal statistical analysis on this was performed.

When looking into the risk factors for RR after surgery for early stage NSCLC, there are two types of studies. Most studies have investigated predictive factors for ONM in clinical stage I NSCLC through examination of the resected specimens of the tumour and the lymph nodes^{11,38-43}. Identified risk factors for ONM include larger tumour size, solid consistency on high-resolution CT, adenocarcinoma, higher SUV_{max}, increased carcinoembryonic antigen level, visceral pleural invasion (VPI), and poor pathological differentiation.

The incidence of occult nodal metastases (pN1 or pN2) for resected clinical stage 1 (cN0) NSCLC varies between 10-20% in most studies, with pN2 rates generally around 5-8%^{11,13,14}. A central location of the tumour can be associated with a higher incidence of pN1 upstaging. Decaluwé *et al.*¹⁴ found pN1 disease to be present in 32.6% of the patients with central (defined as visible tumour by standard video bronchoscopy) clinical stage I NSCLC, irrespective of surgical technique.

The type of intra-operative lymph node evaluation (dissection or sampling) seems to be irrelevant. In the largest and most recent randomised study comparing mediastinal lymph node sampling (MLNS) to lymph node dissection in 1023 evaluable cT1-2N0M0 NSCLC patients, only 4% of the patients who underwent a full nodal dissection after initially negative mediastinal lymph node sampling had mediastinal (N2) nodal disease¹⁵.

OS and recurrence rates were similar between the sampled patients and those patients having received a complete lymph node dissection.

Studies investigating risk factors for RR after surgery in pN0 patients are scarce. A study by Lopez-Guerra and colleagues ⁴⁴ is one of the few. Of 1402 consecutive stage I-III (pN0-pN1) NSCLC patients who underwent a complete resection without adjuvant radiotherapy, 6% developed a RR (4% isolated nodal failure). In multivariate analysis, pN1 status, VPI and lymphovascular space invasion (LVI) were independently significant risk factors for RR. RR occurred in 9% of pN1 *versus* 5% of pN0 patients, 9% of patients with VPI *versus* 5% of those without VPI, 10% of patients with LVI *versus* 5% of those without LVI. Important limitations of the study are that details on the preoperative lymph node staging (PET/CT imaging and/or EBUS and/or mediastinoscopy) and lymph node evaluation during surgery are lacking (systematic lymph node dissection or sampling). Also, the investigated patient cohort consisted of all patients treated with surgery. The portion of cT1-2N0 patients in the study and the incidence of RR within this subgroup are not specified.

DISCUSSION

Over the last decade, SABR has gained ground and has become a valuable addition to the treatment of early stage NSCLC, especially for elderly patients and patients who are inoperable due to comorbid disease or who would rather not undergo surgery ^{7,8}. The aim of the current systematic review was to obtain more information on the incidence of, and risk factors for, regional recurrence after SABR in stage I NSCLC. Patients who undergo SABR lack definite pathological staging of the regional lymph nodes, while in surgically treated patients a systematic lymph node dissection is performed. Theoretically, this could lead to an increased risk of regional recurrence after SABR, as is often stated in the literature ^{26,32,45}. From the included studies, the mean incidence of RR after SABR was found to be almost 10%. In the studies comparing regional control between SABR and surgery, the RR rates were similar, despite the intra-operative systematic mediastinal lymphadenectomy.

When assuming that patients treated with radiotherapy should have more nodal failures than surgical patients, several hypotheses have been mentioned in the literature to explain the lack of difference in regional control. Grills *et al.* ³² suggest incidental dose to the regional nodes, differences in follow-up and a higher non-cancer death rate after SABR to result in possible 'underestimation' of nodal failures. The theory of sterilisation

of micrometastases through incidental mediastinal/hilar dose is supported by the observations of Lao *et al.*¹⁶ amongst others, however, it is still a matter for debate⁴⁶.

An immune modulatory effect of (hypofractionated) radiotherapy is another often postulated explanation for the lower than expected regional failure rates after SABR^{11,16,26,45}. The radiation-induced improved tumour antigen expression, presentation and increased T-cell response supposedly result in antitumour effects outside the treatment field (in for example lymph nodes), the so-called abscopal effect⁴⁷. However, (pre)clinical data describing this tumour vaccination phenomenon after radiotherapy alone are rare: the effect mainly occurs when combining radiotherapy with immunotherapy (e.g. checkpoint inhibitors)⁴⁷⁻⁵⁰.

Another important factor to consider is the extent of lymph node dissection in surgical patients. Compared to lobectomy, fewer lymph nodes are sampled/dissected in sublobar resections^{51,52}. Similarly, fewer nodal stations are sampled by surgeons when a wedge resection is performed instead of a segmentectomy, resulting in a lower rate of nodal upstaging^{51,53,54}. Additionally, it is known that even if a MLND is performed, the extent of the dissection is often inconsistent with available guidelines. Verhagen *et al.*⁵⁵ performed a retrospective cohort study on 216 patients who underwent an intended complete resection for NSCLC (84% lobectomy, 13% pneumonectomy). The authors conclude that only 4% of the patients underwent a complete lymph node dissection according to the guideline of the European Society of Thoracic Surgery for intra-operative lymph node staging. Insufficient or lack of lymph node dissection has been suggested to adversely affect survival in patients treated with surgery for early stage NSCLC^{56,57}.

Clinically occult lymph node metastases are associated with a poorer disease outcome. Rusch *et al.*¹⁷ found occult lymph node metastases diagnosed with immunohistochemistry in NSCLC patients with resected histologically negative lymph nodes (pN0 through haematoxylin and eosin staining) to be significantly associated with a worse disease-free and overall survival (hazard ratio 1.50 and 1.58, respectively, $p=0.031$ and $p=0.009$). Occult nodal metastases are known to be present in 10-20% of the patients with clinical stage I NSCLC who undergo surgery^{11,13,14}. For patients treated with SABR, the rate of occult nodal involvement is of course unknown. Using a cohort of surgically treated stage I NSCLC patients, Robson *et al.*⁵⁸ have attempted to estimate this rate in patients with peripheral tumours, technically suitable for treatment with SABR. Occult mediastinal or hilar nodal involvement was present in 8.9% of lesions suitable for SABR.

We have noticed that the rate of (suspected) ONM in patients with clinical stage I NSCLC approximates the rate of regional recurrences found in the studies included in this

systematic review of almost 10%. That gives rise to the hypothesis that the percentage of nodal failures simply reflects the percentage of occult nodal metastases and that the type of treatment (SABR or surgery plus MLND/MLNS) might not be that relevant. If that is the case, more intensive staging procedures pre-SABR are not likely to reduce nodal failures during follow-up, even though it is well-known that small metastases are likely to be missed with PET/CT^{10,11}. A literature review by Kim *et al.*¹⁰ reported a pooled sensitivity of 41% for the detection of N1 disease, with a wide range of 17-93%. The authors hypothesise that the wide range in sensitivity was (partly) due to the variation in applied threshold of the SUV_{max} between studies.

The concordance of PET/CT with EBUS Transbronchial Needle Aspiration (EBUS-TBNA) for intrathoracic nodal assessment prior to SABR was retrospectively examined by Vial *et al.*⁵⁹. All 246 patients had biopsy proven NSCLC and were potential SABR candidates with a tumour size smaller than 5cm with no clinical radiographic evidence of distant metastasis or mediastinal (N2) nodal disease. Nodal involvement was diagnosed by EBUS-TBNA in 6 of 174 clinical N0 patients (3.4%). Additionally, 6 and 36 of 72 clinical N1 patients were upstaged to N2 or downstaged to N0 disease (8% and 50%). The authors observed no significant difference in clinical outcome (including locoregional recurrence) between SABR patients with clinical radiographic staging alone and the patients staged as 'N0' by additional EBUS-TBNA.

Two ongoing prospective trials are investigating the additive value of EBUS-TBNA after PET/CT prior to SABR (NCT01786590; NCT02719847). If these studies confirm the results of Vial *et al.*⁵⁹ by showing an equally low rate of nodal involvement in patients without mediastinal disease on PET/CT and no decrease in regional failures, then we believe an EBUS-TBNA should not be added to the routine diagnostic work-up of all SABR candidates. The main application of EBUS-TBNA prior to SABR will be to downstage clinical N1 patients, making them suitable for stereotactic radiotherapy (as shown by Vial *et al.*⁵⁹).

Noteworthy, pre-SABR diagnosis of nodal involvement in patients with clinical stage I disease might be more relevant if SABR is applied in fit, operable patients who choose SABR in order to avoid undergoing surgery. Despite the lack of randomised controlled data, it is likely that SABR will be increasingly applied for these patients in good general condition, as evidence of the equivalence of the two therapeutic options is accumulating^{1,60}. Although frail, medically inoperable patients treated with SABR will likely be unable to undergo adjuvant or concurrent chemotherapy in case of nodal involvement, healthy patients in good clinical condition should be given this opportunity.

Adjuvant chemotherapy for node positive disease can result in a 4% benefit in OS, and postoperative radiotherapy for pN2 disease has been suggested to improve OS by an estimated 13%^{19,61}. For this group of patients able to undergo more aggressive treatment, an additional EBUS-TBNA might be worthwhile in case of a high risk of ONM and (consequently) RR.

From all possible risk factors for RR after SABR, which were investigated in the studies included in this systematic review, we can conclude that none of the FDG-PET-related variables reached significance (SUV_{max} pre- or post SABR, time from FDG-PET/CT to start of treatment). However, (incidental) dose to the hilum and/or mediastinum seems to be relevant, as mentioned earlier. Also, males and patients with anaemia are supposedly more prone to develop nodal failures.

From the surgical literature, occult nodal involvement, visceral pleural invasion (VPI) and lymphovascular space invasion (LVI) were denoted as risk factors for RR⁴⁴. Naturally, most of these pathological risk factors cannot be used to define patients at high risk for RR after SABR as they are not known due to the lack of resected tissue. Possibly, VPI forms an exception: it can be estimated for patients undergoing SABR by determining (the extent of) pleural contact on CT.

It is also evident that nodal upstaging is more common in centrally located tumours¹⁴. Two studies included in our review have included central *versus* peripheral tumour location in their analysis on risk factors for RR^{24,25}. Only Bradley *et al.*²⁵ provide a definition of a central lesion (tumour ≤ 2 cm from a mainstem bronchus or oesophagus). Centrally located tumours were not associated with more nodal failures in both of these studies. Therefore, the relevance of a central tumour location in patients treated with SABR remains unclear. Central tumours are also less often treated with SABR due to the increased risk of serious toxicity⁶²⁻⁶⁴. Comparisons in the literature are hampered by the lack of consensus on the definition of a 'central' lesion, as is discussed by Decaluwé *et al.*¹⁴

Summarising the risk factors for RR derived from the included studies on clinically stage I NSCLC patients treated with SABR, it can be stated that they are limited in number and somewhat unspecific. Therefore, a clear subgroup of patients at high risk for nodal failure after stereotactic radiotherapy cannot be defined based on currently available publications. The surgical literature provided limited additional insight.

Salvage treatment for RR can consist of (a combination of) surgery, radiotherapy and/or chemotherapy, depending on the extent of the recurrent disease (isolated nodal failure (INF) or simultaneous local and/or distant failure) and the performance status. In case

of salvage mediastinal radiotherapy in patients previously treated with SABR, the initial incidental mediastinal dose needs to be taken into account. Fortunately, due to the highly conformal dose distribution of SABR to the usually peripherally located tumours, it is often possible to remain below the existing thresholds for mediastinal dose when applying re-irradiation and thereby possibly avoiding serious toxicity⁶⁵. Ward *et al.*⁶⁶ found disease outcome after INF to be unfavourable, with a median OS of 15.3 months. OS was not significantly different between patients with or without salvage mediastinal radiotherapy (1 year OS 73.3% *versus* 55.5%, respectively, $p=0.245$). One year after INF, a third of the patients not retreated with radiotherapy *versus* 74.6% of the re-irradiated patients were alive without disease ($p=0.221$)⁶⁶. Toxicity was mild: no patients experienced a grade 3 event or higher.

Our study has several limitations. Overall, the available literature on nodal recurrences after SABR and surgery was disappointingly limited. Several studies, sometimes high-ranking, had to be disregarded due to lack of a definition of nodal failure or a definition not meeting our criteria. Almost all of the included studies reported on retrospective data (some of which were prospectively gathered), which automatically implicates the possibility of unknown confounding factors. Also, the studies by Robinson *et al.*²⁶ and Crabtree *et al.*³¹ were composed by the same research group. Several other included studies also originate from the same institutes, thus cohorts may partially overlap^{23,25,26,29,31,32,34}. However, there is considerable variation in the number of included patients, treatment period and patient distribution. Therefore, studies on overlapping cohorts from the same research groups were accepted.

CONCLUSION

In conclusion, the true incidence of regional recurrence after SABR and possible risk factors were difficult to determine. Underlying reasons include variable staging procedures, no separation of central and peripheral tumours, a low number of events, unclear definitions of nodal failure, and a low number of studies on the subject.

However, it appears as though the incidence of RR after SABR or surgery is comparable even though this finding is based on mostly retrospective studies in which the majority of patients treated with SABR were inoperable. The only randomised comparison lacked statistical power to detect differences in recurrence patterns, due to the small number of events¹. Ideally, the true equivalence of the treatments on regional control will have to be investigated, preferably in a randomised controlled trial using a clear definition of RR, but the feasibility of such a very large study is low. We believe that for now, there is

no evidence that inoperable clinical stage I patients with no indication of pathological lymph nodes on PET/CT will benefit from more invasive lymph node staging prior to SABR.

ACKNOWLEDGEMENTS

The authors would like to thank Mark Podesta for his help finalising this manuscript.

REFERENCES

1. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *The Lancet Oncology*. 2015;16(6):630-637.
2. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2010;94(1):1-11.
3. Chen H, Louie AV, Boldt RG, Rodrigues GB, Palma DA, Senan S. Quality of Life After Stereotactic Ablative Radiotherapy for Early-Stage Lung Cancer: A Systematic Review. *Clinical lung cancer*. 2015.
4. Louie AV, van Werkhoven E, Chen H, et al. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non-small-cell lung cancer: Results from the ROSEL multicenter randomized trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2015;117(1):44-48.
5. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *International journal of radiation oncology, biology, physics*. 2014;88(5):1092-1099.
6. Zhao J, Yorke ED, Li L, et al. Simple Factors Associated With Radiation-Induced Lung Toxicity After Stereotactic Body Radiation Therapy of the Thorax: A Pooled Analysis of 88 Studies. *International journal of radiation oncology, biology, physics*. 2016;95(5):1357-1366.
7. Peguret N, Dahele M, Lagerwaard F, Senan S, Slotman BJ. A brief report of 10-year trends in the use of stereotactic lung radiotherapy at a dutch academic medical center. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2014;9(1):114-117.
8. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(35):5153-5159.
9. De Leyn P, Dooms C, Kuzdzal J, et al. Preoperative mediastinal lymph node staging for non-small cell lung cancer: 2014 update of the 2007 ESTS guidelines. *Translational lung cancer research*. 2014;3(4):225-233.
10. Kim MP, Correa AM, Hofstetter W, et al. Limitations of 18F-2-deoxy-D-glucose positron emission tomography in N1 detection in patients with pathologic stage II-N1 and implications for management. *The Annals of thoracic surgery*. 2015;99(2):414-420.
11. Li L, Ren S, Zhang Y, et al. Risk factors for predicting the occult nodal metastasis in T1-2N0M0 NSCLC patients staged by PET/CT: potential value in the clinic. *Lung cancer*. 2013;81(2):213-217.
12. Valle LF, Jaggi R, Bobiak SN, et al. Variation in Definitive Therapy for Localized Non-Small Cell Lung Cancer Among National Comprehensive Cancer Network Institutions. *International journal of radiation oncology, biology, physics*. 2016;94(2):360-367.
13. Boffa DJ, Kosinski AS, Paul S, Mitchell JD, Onaitis M. Lymph node evaluation by open or video-assisted approaches in 11,500 anatomic lung cancer resections. *The Annals of thoracic surgery*. 2012;94(2):347-353; discussion 353.
14. Decaluwe H, Stanzi A, Dooms C, et al. Central tumour location should be considered when comparing N1 upstaging between thoracoscopic and open surgery for clinical stage I non-small-cell

- lung cancer. *European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery*. 2016;50(1):110-117.
15. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *The Journal of thoracic and cardiovascular surgery*. 2011;141(3):662-670.
 16. Lao L, Hope AJ, Maganti M, et al. Incidental prophylactic nodal irradiation and patterns of nodal relapse in inoperable early stage NSCLC patients treated with SBRT: a case-matched analysis. *International journal of radiation oncology, biology, physics*. 2014;90(1):209-215.
 17. Rusch VW, Hawes D, Decker PA, et al. Occult metastases in lymph nodes predict survival in resectable non-small-cell lung cancer: report of the ACOSOG Z0040 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2011;29(32):4313-4319.
 18. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013;24 Suppl 6:vi89-98.
 19. Billiet C, Decaluwe H, Peeters S, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2014;110(1):3-8.
 20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer*. 2009;45(2):228-247.
 21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *Journal of the National Cancer Institute*. 2000;92(3):205-216.
 22. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. *European journal of cancer*. 2009;45(2):261-267.
 23. Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2012;7(9):1382-1393.
 24. Nath SK, Sandhu AP, Kim D, et al. Locoregional and distant failure following image-guided stereotactic body radiation for early-stage primary lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011;99(1):12-17.
 25. Bradley JD, El Naqa I, Drzymala RE, Trovo M, Jones G, Denning MD. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. *International journal of radiation oncology, biology, physics*. 2010;77(4):1146-1150.
 26. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2013;8(2):192-201.
 27. Spratt DE, Wu AJ, Adeseye V, et al. Recurrence Patterns and Second Primary Lung Cancers After Stereotactic Body Radiation Therapy for Early-Stage Non-Small-Cell Lung Cancer: Implications for Surveillance. *Clinical lung cancer*. 2016;17(3):177-183 e172.
 28. Ebright MI, Russo GA, Gupta A, Subramaniam RM, Fernando HC, Kachnic LA. Positron emission tomography combined with diagnostic chest computed tomography enhances detection of

- regional recurrence after stereotactic body radiation therapy for early stage non-small cell lung cancer. *The Journal of thoracic and cardiovascular surgery*. 2013;145(3):709-715.
29. Badiyan SN, Bierhals AJ, Olsen JR, et al. Stereotactic body radiation therapy for the treatment of early-stage minimally invasive adenocarcinoma or adenocarcinoma in situ (formerly bronchioalveolar carcinoma): a patterns of failure analysis. *Radiation oncology*. 2013;8:4.
 30. Bollineni VR, Widder J, Pruim J, Langendijk JA, Wiegman EM. Residual (1)(8)F-FDG-PET uptake 12 weeks after stereotactic ablative radiotherapy for stage I non-small-cell lung cancer predicts local control. *International journal of radiation oncology, biology, physics*. 2012;83(4):e551-555.
 31. Crabtree TD, Puri V, Robinson C, et al. Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy. *The Journal of thoracic and cardiovascular surgery*. 2014;147(4):1183-1191; discussion 1191-1182.
 32. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(6):928-935.
 33. Horne ZD, Clump DA, Vargo JA, et al. Pretreatment SUVmax predicts progression-free survival in early-stage non-small cell lung cancer treated with stereotactic body radiation therapy. *Radiation oncology*. 2014;9:41.
 34. Olsen JR, Robinson CG, El Naqa I, et al. Dose-response for stereotactic body radiotherapy in early-stage non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2011;81(4):e299-303.
 35. Shaverdian N, Veruttipong D, Wang J, Kupelian P, Steinberg M, Lee P. Pretreatment Anemia Portends Poor Survival and Nonlocal Disease Progression in Patients with Stage I Non-Small Cell Lung Cancer Treated with Stereotactic Body Radiation Therapy. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(8):1319-1325.
 36. Collins BT, Vahdat S, Erickson K, et al. Radical cyberknife radiosurgery with tumor tracking: an effective treatment for inoperable small peripheral stage I non-small cell lung cancer. *Journal of hematology & oncology*. 2009;2:1.
 37. Saynak M, Veeramachaneni NK, Hubbs JL, et al. Local failure after complete resection of N0-1 non-small cell lung cancer. *Lung cancer*. 2011;71(2):156-165.
 38. Fuwa N, Mitsudomi T, Daimon T, et al. Factors involved in lymph node metastasis in clinical stage I non-small cell lung cancer--from studies of 604 surgical cases. *Lung cancer*. 2007;57(3):311-316.
 39. Cho S, Song IH, Yang HC, Kim K, Jheon S. Predictive factors for node metastasis in patients with clinical stage I non-small cell lung cancer. *The Annals of thoracic surgery*. 2013;96(1):239-245.
 40. Jiang L, Liang W, Shen J, et al. The impact of visceral pleural invasion in node-negative non-small cell lung cancer: a systematic review and meta-analysis. *Chest*. 2015;148(4):903-911.
 41. Ohta Y, Oda M, Wu J, et al. Can tumor size be a guide for limited surgical intervention in patients with peripheral non-small cell lung cancer? Assessment from the point of view of nodal micrometastasis. *The Journal of thoracic and cardiovascular surgery*. 2001;122(5):900-906.
 42. Inoue M, Minami M, Shiono H, Sawabata N, Ideguchi K, Okumura M. Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2 cm or less in diameter: pleural invasion and increase of serum carcinoembryonic antigen level as predictors of nodal involvement. *The Journal of thoracic and cardiovascular surgery*. 2006;131(5):988-993.
 43. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *The Journal of thoracic and cardiovascular surgery*. 2005;130(1):160-165.

44. Lopez Guerra JL, Gomez DR, Lin SH, et al. Risk factors for local and regional recurrence in patients with resected N0-N1 non-small-cell lung cancer, with implications for patient selection for adjuvant radiation therapy. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013;24(1):67-74.
45. Senan S, Palma DA, Lagerwaard FJ. Stereotactic ablative radiotherapy for stage I NSCLC: Recent advances and controversies. *Journal of thoracic disease*. 2011;3(3):189-196.
46. Rwigema JC, Chen AM, Wang PC, Lee JM, Garon E, Lee P. Incidental mediastinal dose does not explain low mediastinal node recurrence rates in patients with early-stage NSCLC treated with stereotactic body radiotherapy. *Clinical lung cancer*. 2014;15(4):287-293.
47. Reynders K, Illidge T, Siva S, Chang JY, De Ruyscher D. The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant. *Cancer treatment reviews*. 2015;41(6):503-510.
48. Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. *CA: a cancer journal for clinicians*. 2016.
49. Popp I, Grosu AL, Niedermann G, Duda DG. Immune modulation by hypofractionated stereotactic radiation therapy: Therapeutic implications. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016;120(2):185-194.
50. Rekers NH, Troost EG, Zegers CM, Germeraad WT, Dubois LJ, Lambin P. Stereotactic ablative body radiotherapy combined with immunotherapy: present status and future perspectives. *Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique*. 2014;18(5-6):391-395.
51. Speicher PJ, Gu L, Gulack BC, et al. Sublobar Resection for Clinical Stage IA Non-small-cell Lung Cancer in the United States. *Clinical lung cancer*. 2016;17(1):47-55.
52. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. *The Journal of thoracic and cardiovascular surgery*. 2014;147(2):754-762; Discussion 762-754.
53. Kent M, Landreneau R, Mandrekar S, et al. Segmentectomy versus wedge resection for non-small cell lung cancer in high-risk operable patients. *The Annals of thoracic surgery*. 2013;96(5):1747-1754; discussion 1754-1745.
54. Altorki NK, Kamel MK, Narula N, et al. Anatomical Segmentectomy and Wedge Resections Are Associated with Comparable Outcomes for Patients with Small cT1N0 Non-Small Cell Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(11):1984-1992.
55. Verhagen AF, Schoenmakers MC, Barendregt W, et al. Completeness of lung cancer surgery: is mediastinal dissection common practice? *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2012;41(4):834-838.
56. Stiles BM, Kamel MK, Nasar A, et al. The importance of lymph node dissection accompanying wedge resection for clinical stage IA lung cancerdagger. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2016.
57. Wang X, Yan S, Phan K, et al. Mediastinal lymphadenectomy fulfilling NCCN criteria may improve the outcome of clinical N0-1 and pathological N2 non-small cell lung cancer. *Journal of thoracic disease*. 2016;8(3):342-349.
58. Robson JM, Vaidyanathan S, Cheyne L, Snee M, Franks K, Callister ME. Occult nodal disease in patients with non-small-cell lung cancer who are suitable for stereotactic ablative body radiation. *Clinical lung cancer*. 2014;15(6):466-469.

59. Vial MR, Khan KA, O'Connell O, et al. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Nodal Staging of Stereotactic Ablative Body Radiotherapy Patients. *The Annals of thoracic surgery*. 2016.
60. Verstegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2013;24(6):1543-1548.
61. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *The Cochrane database of systematic reviews*. 2015(3):CD011430.
62. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(30):4833-4839.
63. Tekatli H, Haasbeek N, Dahele M, et al. Outcomes of Hypofractionated High-Dose Radiotherapy in Poor-Risk Patients with "Ultracentral" Non-Small Cell Lung Cancer. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer*. 2016;11(7):1081-1089.
64. Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. *Practical radiation oncology*. 2016;6(2):e27-33.
65. Kilburn JM, Lester SC, Lucas JT, Jr., et al. Management of mediastinal relapse after treatment with stereotactic body radiotherapy or accelerated hypofractionated radiotherapy for stage I/II non-small-cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2014;9(4):572-576.
66. Ward MC, Oh SC, Pham YD, et al. Isolated Nodal Failure after Stereotactic Body Radiotherapy for Lung Cancer: The Role for Salvage Mediastinal Radiotherapy. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(9):1558-1564.

CHAPTER 3

Contact of a tumour with the pleura is not associated with regional recurrence following stereotactic ablative radiotherapy for early stage non-small cell lung cancer.

Krista C.J. Wink, Steffen Löck, Maddalena Rossi, Angela van Baardwijk, José Belderbos, Dirk de Ruysscher, Esther G.C. Troost

Radiotherapy & Oncology 2019; 131: 120-126

ABSTRACT

Background and purpose

The aim was to investigate the incidence of isolated regional failure following stereotactic ablative radiotherapy (SABR) and risk factors for recurrence.

Materials and methods

Early stage non-small cell lung cancer (NSCLC) patients treated with SABR were included in this retrospective cohort study, with isolated regional recurrence (IRR) as primary endpoint, distant recurrence (DR) and overall survival (OS) as secondary endpoints. Survival analyses were performed using the cumulative incidence function (IRR and DR) or the Kaplan-Meier method (OS) and Cox proportional hazards modelling for univariate and multivariate analyses. The prognostic effect of contact between the tumour and the pleura was investigated using the CT scans used for SABR planning.

Results

A total of 554 patients were included, of whom 494 could be analysed for IRR. The median follow-up for surviving patients was 48.1 months. Twenty-one patients developed an IRR (4%). The cumulative incidence of IRR and DR after 1-, 2-, and 5 years was 2%, 3%, 7% and 8%, 15% and 21%, respectively. Two year OS was 71%. The presence and type of pleural contact was not associated with any of the studied outcomes.

Conclusion

The presence, type and length of pleural contact as surrogate for visceral pleural invasion were not predictive for outcome. Further studies focussing on risk factors for occult nodal involvement, (I)IRR, distant metastases and mortality in early stage NSCLC are warranted for the development of risk adapted diagnostic, treatment and follow-up strategies as more younger, operable and fitter patients receive SABR.

INTRODUCTION

Stereotactic ablative body radiotherapy (SABR) of early stage non-small cell lung cancer (NSCLC) has been shown to result in excellent local control rates of more than 90%¹. The predominant site of failure is distant, with approximately 20% of the patients developing distant metastases within 3 years¹. Regional lymph node recurrence (RR) following SABR occurs in approximately 10% of the patients and predominantly involves lymph node stations 4, 7 or 10²⁻⁵. An isolated regional recurrence (IRR) can potentially be treated with curative-intent surgery or radiotherapy, possibly complemented with (concurrent) chemotherapy depending on disease stage⁶⁻⁸. The identification of patients at high risk of occult nodal disease and regional recurrence is desirable when defining the diagnostic work-up prior to SABR and risk-based follow-up regimens following SABR, especially as more younger and fitter patients are receiving SABR. These patients are more likely able to undergo adjuvant systemic treatment in case of a high disease recurrence risk and/or salvage treatment in case of an IRR compared to the traditionally elderly, inoperable SABR population.

In multiple studies, attempts have been made to identify risk factors for the development of a regional recurrence, as summarised in a recent systematic review². Hampered by the predominantly retrospective nature of the studies, variable staging procedures, a low number of events and unclear definitions of nodal failure, a subgroup of patients at high risk for regional recurrence could not be defined. Anaemia, male gender and incidental dose to the regional lymph nodes were found to be relevant. The surgical literature has provided risk factors such as occult nodal involvement, lymphovascular space invasion (LVI), and visceral pleural invasion (VPI)². A suggested route for lymph node metastases originating from a tumour with VPI is subpleural lymphatic drainage of tumour cells from the pleural cavity through the hilar lymph nodes and/or diaphragmatic lymphatics into the mediastinal lymph nodes^{9,10}. As VPI and LVI are determined on resected specimens, they cannot hold predictive value for patients undergoing SABR. However, the presence of VPI can be predicted using thoracic CT images¹¹.

The aim of this large multi-institutional retrospective study was to describe patterns of nodal failure following SABR and to identify patient-, tumour- and treatment-related risk factors for IRR. The prognostic value of the relation of the tumour to the visceral pleura was investigated retrospectively using the CT scans for SABR planning.

MATERIALS AND METHODS

Patients and treatment

All patients included in this retrospective cohort study were treated with image-guided SABR between 2007 and 2015, in one of three international institutions: MAASTRO clinic (MC, the Netherlands), the Netherlands Cancer Institute (NKI, the Netherlands), or the University Hospital Carl Gustav Carus of the Technische Universität Dresden (UHCGC, Germany). Patients were staged with a total-body ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). Mediastinal lymph node staging with endobronchial ultrasound (EBUS) or mediastinoscopy was performed at the discretion of the treating physician, depending on the (PET)/CT findings. A clinical diagnosis of (assumed) cT1-3, N0, M0 NSCLC based on serial CT imaging and/or PET/CT results was required for treatment. Histologic proof of malignancy was pursued whenever possible, but neither required for SABR (when fulfilling the aforementioned criteria) nor for inclusion in the current study. SABR was performed following the local practice guidelines for treatment planning and delivery at each institution, including daily image guidance. Various treatment planning techniques were used, including fixed-beam and arc-techniques based on forward- or inverse-planning. Follow-up imaging was performed in accordance with local and national guidelines, typically consisting of a CT scan within 6 weeks to 4 months after SABR and annually thereafter. If disease recurrence (local, regional or distant) was suspected, a PET/CT and/or biopsy were usually performed if clinically relevant.

The following exclusion criteria were applied: multiple lung tumours, non-NSCLC histology (small cell lung cancer, pulmonary metastases from other primary tumours), previous treatment with intrathoracic surgery or intrathoracic radiotherapy for cancer (with the exception of whole breast irradiation), treatment for any type of cancer (excluding basal cell carcinoma of the skin) less than two years prior to SABR, a maximum tumour diameter (MTD) of more than 6 cm, and a Biologically Effective Dose (BED) <95Gy.

Assessment of pleural contact

To avoid differences in outcome due to measuring inconsistencies, the MTD and presence and type of pleural contact were ascertained and measured by one researcher (KW) in all three institutions. For all measurements, the standard lung-window setting was used on the CT. For tumours abutting the pleura, the maximum pleural distance (MPD) constituted the maximum length of pleural contact in the axial, sagittal or coronal plane (Figure 1). In case of multiple sites of pleural contact (for example the interlobar fissure and the pleura lining the thoracic wall), the maximum length of contact of each site added up to the cumulative MPD. Consequently, an MPD larger than the MTD was

possible. Furthermore, three types of pleural tags were identified for tumours in contact with, but not abutting, the pleura: 1) a linear tag on lung window, 2) a tag on mediastinal window with a soft tissue component at the pleural end or 3) a cord-like tag on mediastinal window¹² (Figure 2).

Figure 1: The maximum pleural distance (MPD) was measured in three directions, of which the largest distance was used for the analyses. This figure shows examples of measurements for: A) a tumour in contact with the thoracic wall (axial view) and B,C,D) a tumour in contact with the interlobar fissure, in all three measuring directions (coronal, axial, sagittal)

Figure 2: Types of pleural tags: A) linear pleural tag on lung window, B) linear pleural tag with soft-tissue component at pleural end on mediastinal window, C) cord-like pleural tag on mediastinal window.

Outcomes and statistical analyses

Isolated regional recurrence was considered our primary endpoint, distant recurrence (DR) and overall survival (OS) were secondary endpoints. IRR was defined as a new or growing lymph node on CT combined with FDG-PET avidity, and/or a biopsy confirmed regional recurrence and/or continuing lymph node enlargement on serial CT scans (lymph node $\geq 1\text{cm}$)². Patients with an IRR had no evidence of distant metastases within 2 months after diagnosis of the nodal recurrence. As it is challenging to ascertain a local recurrence (LR) following SABR due to heterogeneous radiographic changes, the local disease status was not assessed. Therefore, patients with an IRR could have a simultaneous LR, still representing a potentially curable disease stage. Time to recurrence and survival were calculated from the first day of stereotactic radiotherapy. For IRR, patients were censored at the date of the last acquired (PET/CT). For DR, patients were censored at the date of last contact with a physician. OS data was collected from a Dutch or German national database. The patients from UHCGC were included in the overall survival analyses only, since follow-up data on the course of the disease (occurrence of IRR and/or DR) were not retrievable from the referring centres.

Survival analyses were performed using the Kaplan-Meier method (OS) or the cumulative incidence function (IRR and DR). Cox proportional hazards modelling was used for univariate and multivariate analyses, to test the prognostic significance of several patient and tumour related variables, e.g. tumour size, patient age and performance status, the use of metformin at the time of SABR¹³. The following variables describing the relation of the tumour with the pleura were evaluated: the type of pleural contact (no contact, pleural tag or tumour abutting the pleura), the MPD (as continuous variable and dichotomised in two categories using the median distance) and the MPD/MTD ratio¹¹. An overall chi-squared test was performed for categorical variables with more than two factors. Variables with significant correlation to outcome in univariate analysis were entered in multivariate models. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 24 (IBM Corporation, Armonk, NY).

RESULTS

In total 554 patients met the inclusion criteria. Patient and treatment characteristics are given in Table 1. The median follow-up for all patients was 36.1 months (range 1.1-118.3 months) and 48.1 months (range 26.6-118.3 months) for surviving patients. For IRR, the median FU was 20.0 months (range 1.1-108.3 months). The median patient age was 74 years (range 42-91 years), 58% were male and 64% had a good general performance (WHO score 0 or 1). A total 545 patients (98%) were staged with a pre-treatment FDG-

PET/CT. Sixty-eight percent of the patients (377/554) received SABR on a suspicion of malignancy without histological proof. The median prescribed dose was 54 Gy (range 45 – 75Gy in 3-8 fractions). Most lung tumours were peripherally located and 66% were situated in one of the upper lobes (365/554). Seventy-nine percent (439/554) had some form of pleural contact (pleural tag or tumour abutting the pleura). Median MPD was 23mm (range 6-79mm), consisting of two measurements in 13 patients.

Table 1: Patient characteristics.

Parameter	Number of patients (%)
Institution	102 / 60 / 392
MAASTRO clinic / UHCGC / NKI	(18.4 / 10.8 / 70.8)
Gender	320 / 234
male / female	(57.8 / 42.2)
Location	209 / 156 / 104 / 66 / 18
RUL / LUL / RLL / LLL / RML	(37.7 / 28.2 / 18.8 / 11.9 / 3.2)
Histology	66 / 66 / 28 / 3 / 14 / 377
ACC / SCC / LCC / AIS / NSCLC NOS / none	(11.9 / 11.9 / 5.1 / 0.5 / 2.5 / 68.1)
cT Stage	428 / 124 / 2
1 / 2 / 3	(77.2 / 22.4 / 0.4)
WHO PS	85 / 269 / 161 / 23 / 3 / 13
0 / 1 / 2 / 3 / 4 / unknown	(15.3 / 48.6 / 29.1 / 4.2 / 0.5 / 2.3)
Metformin	462 / 66 / 26
no / yes / unknown	(83.4 / 11.9 / 4.7)
Pleural contact	79 / 244 / 195 / 36
no / pleural tag / tumour abuts pleura / unknown	(14.3 / 44.0 / 35.2 / 6.5)
Pleural tag type (n=244)	65 / 84 / 92 / 3
Linear lung / linear mediastinal / cord-like mediastinal / undefined	(26.6 / 34.4 / 37.7 / 1.2)
Pleural distance (n=195)	93 / 86 / 16
MPD ≤23 mm / MPD >23 mm / unmeasurable	(47.7 / 44.1 / 8.2)
Parameter	Median (range)
Age (years)	74.0 (42.0-91.0)
BMI (kg/m²)	24.6 (12.3-51.2)
GTV (ml)	6.0 (0.3-95.3)
EQD2 95% (Gy)	115.9 (81.3-200.4)
MPD (mm)	23.0 (6.0-79.0)

ACC = adenocarcinoma, AIS = adenocarcinoma in situ (former bronchoalveolar carcinoma), BMI = Body Mass Index, EQD2 95% = 95% of the prescribed dose as an equivalent dose of 2Gy fractions, using an α/β ratio of 10 Gy for the tumour, GTV = gross tumour volume, LCC = large cell carcinoma, LLL = left lower lobe, LUL = left upper lobe, MPD = maximum pleural distance, NKI = National Cancer Institute, NSCLC NOS = non-small cell lung cancer not otherwise specified, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe, SCC= squamous cell carcinoma, UHCGC = University Hospital Carl Gustav Carus, WHO PS = World Health Organization Performance Score.

Clinical outcomes

A total 494/554 patients were analysed for incidence of IRR. A regional lymph node recurrence was diagnosed in 39 patients (8%) and distant metastases in 91 patients (18%). Of the 39 patients with a RR, 22 were also diagnosed with a DR (56%), of whom 18 prior or synchronous to the RR (46%). Therefore, the incidence of IRR was 4% (21/494). In 76% (16/21), the upper mediastinum was involved (lymph node stations 2-4), in 48% (10/21) the lower mediastinum (stations 5-8), in 19% (4/21) the ipsilateral hilar region, in 14% (3/21) the contralateral hilar region and in 5% (1/21) the supraclavicular region. The median time to both IRR and DR was not reached. The 1-, 2- and 5-year cumulative incidence of IRR and DR were 2%, 3%, 7% and 8%, 15% and 21%, respectively (Figure 3A and B). The 2- and 5-year overall survival rates were 71% and 47%, respectively, and the median overall survival time following SABR was 54 months (Figure 4). Best supportive care was given to 43% of patients with an isolated nodal recurrence (9/21), 7 patients (33%) were radically treated with either radiotherapy alone or sequential or concurrent chemoradiotherapy, 2 patients (10%) received systemic therapy only and for 3 patients (14%) the treatment was unknown.

Figure 3: Cumulative incidence function of A) isolated regional recurrence (IRR) and B) distant recurrence (DR).

Figure 4: Kaplan-Meier estimate of overall survival.

The results of the univariate and multivariate analyses for IRR, DR and OS are presented in Tables 2, 3 and 4. The presence and extent of pleural contact were not associated with IRR or any of the other studied outcomes, including RR (data on RR not shown). While a younger age and a smaller GTV were significantly associated with less IRR in univariable analysis, their significance was lost in multivariable analysis. The cT-stage did correlate significantly with DR (cT1 superior to cT2/cT3, $p < 0.001$). A total 66/554 patients were using metformin at the time of SABR. Metformin use did not result in improved outcomes following SABR.

Table 2: Univariable Cox regression for isolated regional recurrence and distant recurrence.

Parameter	Isolated regional recurrence		Distant recurrence	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.06 (1.00-1.12)	0.033	1.02 (0.99-1.04)	0.18
Gender (male / female)	0.57 (0.24-1.39)	0.22	0.91 (0.60-1.38)	0.67
cT (1 vs 2,3)	0.85 (0.25-2.91)	0.80	3.01 (1.96-4.63)	<0.001
WHO PS (0,1 vs 2,3)	0.48 (0.14-1.64)	0.24	1.18 (0.75-1.83)	0.48
BMI (kg/m ²)	0.96 (0.88-1.06)	0.42	0.99 (0.94-1.03)	0.54
Metformin (no / yes)	1.04 (0.30-3.55)	0.95	1.19 (0.66-2.14)	0.57
Location		**	**	
GTV (ml)	1.03 (1.00-1.06)	0.029	1.03 (1.01-1.04)	<0.001
EQD2 95% (Gy)	0.98 (0.95-1.01)	0.24	1.01 (0.99-1.03)	0.42
Pleural contact (none / tag / tumour abuts pleura)		0.28	*	0.55
Pleural contact (none / present)	1.01 (0.29-3.56)	0.98	1.38 (0.75-2.54)	0.31
Pleural tag type (linear lung / linear mediastinal / cord-like mediastinal)		0.64	*	0.25
Pleural categories (remaining vs MPD > 23 mm)	1.86 (0.52-6.61)	0.34	1.44 (0.82-2.53)	0.20
MPD (mm)	1.02 (0.97-1.08)	0.37	1.03 (1.01-1.06)	0.006
MPD/MTD ratio	5.25 (0.42-65.8)	0.20	2.70 (0.66-11.1)	0.17

BMI = Body Mass Index, EQD2 95% = 95% of the prescribed dose as an equivalent dose of 2Gy fractions, using an α/β ratio of 10 Gy for the tumour, GTV = gross tumour volume, HR = hazard ratio, MPD = maximum pleural distance, MTD = maximum tumour diameter, RML = right middle lobe, WHO PS = World Health Organization Performance Score.

*overall chi-squared test of categorical variables with more than two factors

** no convergence (no event in RML group)

Table 3: Multivariable Cox regression for isolated regional recurrence and distant recurrence.

Parameter	Isolated regional recurrence		Distant recurrence	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.04 (0.99-1.10)	0.12		
cT (1 vs 2,3)			2.87 (1.67-4.94)	<0.001
GTV (ml)	1.03 (0.99-1.06)	0.10	1.01 (0.98-1.03)	0.64

GTV = gross tumour volume, HR = hazard ratio.

Table 4: Uni- and multivariable Cox regression for overall survival.

Parameter	UVA		MVA	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.02 (1.01-1.04)	<0.001	1.03 (1.02-1.04)	<0.001
Gender (male / female)	0.93 (0.73-1.18)	0.55		
cT (1 vs 2,3)	1.22 (0.92-1.60)	0.17		
WHO PS (0,1 vs 2,3)	2.29 (1.80-2.90)	<0.001	2.40 (1.86-3.09)	<0.001
BMI (kg/m ²)	0.98 (0.96-1.01)	0.15		
Metformin (no / yes)	0.84 (0.57-1.23)	0.36		
Location	*	0.45		
GTV (ml)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.003
EQD2 95% (Gy)	0.99 (0.99-1.00)	0.20		
Pleural contact (none / tag / tumor abuts pleura)	*	0.14		
Pleural contact (none / present)	1.33 (0.93-1.89)	0.12		
Pleural tag type (Linear lung / linear mediastinal / cord-like mediastinal)	*	0.87		
Pleural categories (remaining vs MPD > 23 mm)	1.87 (1.39-2.50)	<0.001	1.40 (0.98-1.98)	0.062
MPD (mm)	1.03 (1.01-1.04)	<0.001		
MPD/MTD ratio	1.67 (0.77-3.63)	0.20		

BMI = Body Mass Index, EQD2 95% = 95% of the prescribed dose as an equivalent dose of 2Gy fractions, using an α/β ratio of 10 Gy for the tumour, GTV = gross tumour volume, HR = hazard ratio, MPD = maximum pleural distance, MTD = maximum tumour diameter, MVA = multivariate analysis, UVA = univariate analysis, WHO PS = World Health Organization Performance Score.

*overall chi-squared test of categorical variables with more than two factors

DISCUSSION

To the best of our knowledge, the current study is the largest to date analysing the incidence of isolated regional recurrence following SABR for NSCLC and the prognostic value of the type and extent of contact between the tumour and the pleura. The overall incidence of IRR as first recurrence was 4% and the overall RR rate was 8%, which is comparable to the IRR and RR rates reported in the literature^{2,4,7}.

From the surgical literature, VPI is a known poor prognostic factor in early stage NSCLC. A negative impact of VPI has been reported on lung cancer specific and overall survival, a higher incidence of involved lymph nodes on lymph node dissection and a higher incidence of lymph node recurrence^{9,14-18}. Consequently, it has remained a pathologic descriptor for T2 staging in the 8th edition of the Union Internationale Contre le Cancer (UICC) TNM classification of malignant lung tumours^{19,20}. As resected tissue is lacking in patients treated with SABR, we measured and calculated the MPD and the MPD/MTD ratio as a surrogate for VPI. As shown by Imai *et al.*¹¹, this ratio as measured on a CT scan

correlates with the extent of pleural invasion on pathologic examination. In their study, a ratio of 0.9 resulted in a high sensitivity and specificity for thoracic invasion of 89.7% and 96%, respectively. In the current study, a prognostic effect of the MPD and/or the MPD/MTD ratio could not be demonstrated for any of the studied outcomes on multivariable analysis. Yamamoto *et al.*²¹ conducted a smaller but similar study to ours, measuring the length of pleural contact on pre-SABR CT images of 87 patients with stage I NSCLC. They found a broad attachment to the pleura of >14.7 mm (the median length of contact) to be a negative independent predictor for locoregional control. We did not find evidence to support their conclusion within our large multi-institutional patient cohort. A possible reason why, in contrast to surgical series, a relation between pleural invasion and regional control was not found could be the sterilisation of involved pleura or tumour cells in the pleural cavity as dose deposition continues outside the PTV.

Several other relevant patient, tumour and (pre-)treatment characteristics were tested for a correlation with (isolated) regional and distant recurrence. None of the tested variables was predictive for (I)RR and only a higher cT stage was significantly associated with DR.

We believe further investigation on the prediction of the outcome of patients treated with SABR is warranted, especially as more younger, fitter and operable patients are receiving stereotactic radiotherapy. The main reason for this is the risk of undertreating those patients who are potentially operable and able to undergo adjuvant systemic treatment in case of high risk features predisposing them to regional or distant disease recurrence. In a recent retrospective cohort study, adjuvant systemic therapy was associated with less regional and distant failures in the SABR population²². Furthermore, the consequence of the lack of final pathological mediastinal staging in patients treated with SABR is largely unknown. A lobectomy or segmentectomy typically includes a systematic lymph node dissection and in case of lymph node involvement, adjuvant systemic therapy is considered²⁰. The available evidence generally does not show an increased risk of RR in patients treated with SABR^{2,23,24}. Suggested explanations include incidental mediastinal/hilar dose from SABR (causing sterilisation of micrometastases), mediastinal lymph node dissections inconsistent with available guidelines, differences in follow-up and a higher non-cancer death rate following SABR². However, van den Berg *et al.*²⁵ reported more locoregional failures and a trend for more nodal failures following SABR. As the data on nodal failure rates comes from mainly retrospective studies in typically medically inoperable patients, the subject remains a matter of debate². Long-term prospective follow-up data on large cohorts of fit, operable patients receiving SABR is still lacking^{2,26}. A pooled analysis of two preliminary closed randomised controlled trials comparing surgery with SABR for operable early stage NSCLC reported

no significant difference in regional and distant control, but was underpowered due to the very small number of patients that entered the trials and small number of events²⁴. The recently published NRG Oncology Radiation Therapy Oncology Group (RTOG) 0618 trial also showed favourable results with a 4-year locoregional control rate of 88% in operable patients treated with SABR²⁷. However, only 26 patients were analysed in this small single-arm phase 2 trial. Several studies are still ongoing attempting to compare SABR with surgical resection in randomised clinical trials (e.g. VALOR, STABLE-MATES, SABRTOOTH)²⁶. If successful, these trials can deliver evidence on the likelihood of equivalence of SABR and surgery with respect to RR and the possible consequences of the lack of final pathologic mediastinal staging.

Currently, clinical staging procedures for SABR are comparable to preoperative staging procedures for early stage NSCLC. No additional preoperative mediastinal staging procedures are recommended in patients staged as cN0 through PET/CT with a tumour ≤ 3 cm located in the outer third of the lung²⁸. This recommendation is based on a high negative predictive value of $>90\%$ of PET/CT and a very low incidence of pN2 disease of 2.9% for peripheral tumours ≤ 3 cm²⁸. As the majority of pulmonary nodules treated with SABR is small and peripherally located, it is not surprising that the yield of pre-SABR invasive mediastinal nodal staging (IMNS) with EBUS or mediastinoscopy is minimal in unselected patients: only 3.4% of cN0 patients (based on PET/CT) are upstaged by IMNS²⁹. Schonewolf *et al.*³ reported similar patterns of failure and overall survival following SABR for patients staged as cN0 with PET/CT combined with IMNS compared to patients staged with PET/CT alone. However, as again mainly medically inoperable patients who are more likely to die from non-oncologic causes were included in these studies, it is unclear whether these results can be extrapolated to a medically operable population.

The indications for SABR are expanding with larger (>5 cm) and more centrally located tumours harbouring a risk of nodal involvement of over 10%³⁰⁻³². This, combined with more younger, potentially operable patients receiving SABR, highlights the importance of future studies focussing on improving outcome prediction by incorporating relevant risk factors for recurrence following stereotactic radiotherapy in prediction models. Subsequently, these models can be used to revise mediastinal staging and follow-up strategies and specify the role of adjuvant systemic therapy following SABR^{22,30,31,33,34}. In addition, more sensitive (mediastinal) staging procedures might improve staging accuracy and should be investigated. Possibilities include a staging 4D PET/CT or the combination of PET/CT and Dual Energy CT imaging (www.clinicaltrials.gov, NCT03146117)³⁵.

The retrospective nature of our study has a few limitations. A lack of (systematic) follow-up and the considering of death as a competing risk may have resulted in an underestimation of regional and distant failures: the (regional) disease status at time of death was not recorded if patients were lost to follow-up and OS data were retrieved from a national database. The 60 patients from the UHCGC (11% of the cohort) could not be analysed for (I)RR and DR. However, we believe it to be unlikely that inclusion of these patients in the IRR analyses would have changed our conclusions.

Almost seventy percent of patients were irradiated without histological proof of malignancy. This is quite common in clinical practice, as the risk of a CT-guided needle biopsy complication such as a pneumothorax and/or haemorrhage is considerable and unfortunate in frail, elderly patients with poor pulmonary function. Thus, often, these patients are being offered SABR without histological proof^{36,37}. The inclusion of T2 and T3 tumours could have led to a higher rate of nodal involvement than if only T1 tumours had been included. The retrospective nature of the study entails a lack of standardisation (e.g. missing information on the management of suspected lymph nodes with respect to biopsy and/or follow-up) and could have given rise to unknown confounding factors. Finally, we attempted to keep the measuring inconsistencies as low as possible by having only one researcher measure the MPDs and MTDs, nevertheless, slight inaccuracies cannot be excluded.

CONCLUSION

In conclusion, the presence, type and length of pleural contact as surrogate for visceral pleural invasion were not predictive for regional and distant recurrence in patients with early stage NSCLC treated with SABR in the current study. Further studies focussing on risk factors for occult nodal involvement, RR, distant metastases and mortality in early stage NSCLC treated with SABR are warranted for the development of risk adapted diagnostic, treatment and follow-up strategies as more younger, operable and fitter patients receive SABR.

REFERENCES

1. Chi A, Liao Z, Nguyen NP, Xu J, Stea B, Komaki R. Systemic review of the patterns of failure following stereotactic body radiation therapy in early-stage non-small-cell lung cancer: clinical implications. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2010;94(1):1-11.
2. Wink KCJ, van Baardwijk A, Troost EGC, De Ruyscher D. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. *Cancer Treat Rev*. 2017;56:8-15.
3. Schonewolf CA, Verma V, Post CM, et al. Outcomes of invasive mediastinal nodal staging versus positron emission tomography staging alone for early-stage non-small cell lung cancer treated with stereotactic body radiation therapy. *Lung cancer*. 2017.
4. Giuliani ME, Hope A, Mangona V, et al. Predictors and Patterns of Regional Recurrence Following Lung SBRT: A Report From the Elekta Lung Research Group. *Clinical lung cancer*. 2017;18(2):162-168.
5. Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: Results of a phase 2 clinical trial. *Cancer*. 2017;123(16):3031-3039.
6. Ward MC, Oh SC, Pham YD, et al. Isolated Nodal Failure after Stereotactic Body Radiotherapy for Lung Cancer: The Role for Salvage Mediastinal Radiotherapy. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(9):1558-1564.
7. Brooks ED, Sun B, Feng L, et al. Association of long-term outcomes and survival with multidisciplinary salvage treatment for local and regional recurrence after stereotactic ablative radiotherapy for early-stage lung cancer. *JAMA Network Open*. 2018;1(4):e181390.
8. Matsuo Y. A Systematic Literature Review on Salvage Radiotherapy for Local or Regional Recurrence After Previous Stereotactic Body Radiotherapy for Lung Cancer. *Technology in cancer research & treatment*. 2018;17:1533033818798633.
9. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2005;130(1):160-165.
10. Okiemy G, Foucault C, Avisse C, Hidden G, Riquet M. Lymphatic drainage of the diaphragmatic pleura to the peritracheobronchial lymph nodes. *Surgical and radiologic anatomy : SRA*. 2003;25(1):32-35.
11. Imai K, Minamiya Y, Ishiyama K, et al. Use of CT to evaluate pleural invasion in non-small cell lung cancer: measurement of the ratio of the interface between tumor and neighboring structures to maximum tumor diameter. *Radiology*. 2013;267(2):619-626.
12. Hsu JS, Han IT, Tsai TH, et al. Pleural Tags on CT Scans to Predict Visceral Pleural Invasion of Non-Small Cell Lung Cancer That Does Not Abut the Pleura. *Radiology*. 2016;279(2):590-596.
13. Wink KC, Belderbos JS, Dieleman EM, et al. Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016;118(3):453-459.
14. Inoue M, Minami M, Shiono H, Sawabata N, Ideguchi K, Okumura M. Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2 cm or less in diameter: pleural invasion and increase of serum carcinoembryonic antigen level as predictors of nodal involvement. *The Journal of thoracic and cardiovascular surgery*. 2006;131(5):988-993.

15. Jiang L, Liang W, Shen J, et al. The impact of visceral pleural invasion in node-negative non-small cell lung cancer: a systematic review and meta-analysis. *Chest*. 2015;148(4):903-911.
16. Kudo Y, Saji H, Shimada Y, et al. Impact of visceral pleural invasion on the survival of patients with non-small cell lung cancer. *Lung cancer*. 2012;78(2):153-160.
17. Lopez Guerra JL, Gomez DR, Lin SH, et al. Risk factors for local and regional recurrence in patients with resected N0-N1 non-small-cell lung cancer, with implications for patient selection for adjuvant radiation therapy. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2013;24(1):67-74.
18. Yang X, Sun F, Chen L, et al. Prognostic value of visceral pleural invasion in non-small cell lung cancer: A propensity score matching study based on the SEER registry. *Journal of surgical oncology*. 2017;116(3):398-406.
19. Travis WD, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposal for the 7th edition of the TNM classification for lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2008;3(12):1384-1390.
20. Goldstraw P, Chansky K, Crowley J, 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. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2016;11(1):39-51.
21. Yamamoto T, Kadoya N, Shirata Y, et al. Impact of tumor attachment to the pleura measured by a pretreatment CT image on outcome of stage I NSCLC treated with stereotactic body radiotherapy. *Radiation oncology*. 2015;10:35.
22. Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2018.
23. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. *The Annals of thoracic surgery*. 2015;99(4):1122-1129.
24. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637.
25. van den Berg LL, Klinkenberg TJ, Groen HJ, Widder J. Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2015;10(5):826-831.
26. Tandberg DJ, Tong BC, Ackerson BG, Kelsey CR. Surgery versus stereotactic body radiation therapy for stage I non-small cell lung cancer: A comprehensive review. *Cancer*. 2018;124(4):667-678.
27. Timmerman RD, Paulus R, Pass HI, et al. Stereotactic Body Radiation Therapy for Operable Early-Stage Lung Cancer: Findings From the NRG Oncology RTOG 0618 Trial. *JAMA oncology*. 2018;4(9):1263-1266.
28. De Leyn P, Doooms C, Kuzdzal J, et al. Preoperative mediastinal lymph node staging for non-small cell lung cancer: 2014 update of the 2007 ESTS guidelines. *Translational lung cancer research*. 2014;3(4):225-233.
29. Vial MR, Khan KA, O'Connell O, et al. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration in the Nodal Staging of Stereotactic Ablative Body Radiotherapy Patients. *The Annals of thoracic surgery*. 2017;103(5):1600-1605.
30. Gao SJ, Kim AW, Puchalski JT, et al. Indications for invasive mediastinal staging in patients with early non-small cell lung cancer staged with PET-CT. *Lung cancer*. 2017;109:36-41.

31. Schneider BJ, Daly ME, Kennedy EB, et al. Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2018;36(7):710-719.
32. Lee PC, Port JL, Korst RJ, Liss Y, Meherally DN, Altorki NK. Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *The Annals of thoracic surgery*. 2007;84(1):177-181.
33. Jumeau R, Bahig H, Filion E, et al. Assessing the Need for Adjuvant Chemotherapy After Stereotactic Body Radiation Therapy in Early-stage Non-small Cell Lung Carcinoma. *Cureus*. 2016;8(11):e901.
34. Harris JP, Nwachukwu C, Qian Y, et al. Invasive nodal evaluation prior to stereotactic ablative radiation for non-small cell lung cancer. *Lung cancer*. 2018;124:76-85.
35. Sindoni A, Minutoli F, Pontoriero A, Iati G, Baldari S, Pergolizzi S. Usefulness of four dimensional (4D) PET/CT imaging in the evaluation of thoracic lesions and in radiotherapy planning: Review of the literature. *Lung cancer*. 2016;96:78-86.
36. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Annals of internal medicine*. 2011;155(3):137-144.
37. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(35):5153-5159.

CHAPTER 4

Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy

Krista C.J. Wink, José S.A. Belderbos, Edith M.T. Dieleman, Maddalena Rossi,
Coen R.N. Rasch, Ronald A.M. Damhuis, Ruud M.A. Houben, Esther G.C. Troost

Radiotherapy & Oncology 2016; 118: 453-459

ABSTRACT

Background and purpose

The aim was to investigate whether the use of metformin during concurrent chemoradiotherapy (cCRT) for locally advanced non-small cell lung cancer (NSCLC) improved treatment outcome.

Material and methods

A total of 682 patients were included in this retrospective cohort study (59 metformin users, 623 control patients). All received cCRT in one of three participating radiation oncology departments in the Netherlands between January 2008 and January 2013. Primary endpoint was locoregional recurrence free survival (LRFS), secondary endpoints were overall survival (OS), progression-free survival (PFS) and distant metastasis free survival (DMFS).

Results

No significant differences in LRFS or OS were found. Metformin use was associated with an improved DMFS (74% versus 53% at 2 years; $p=0.01$) and PFS (58% versus 37% at 2 years and a median PFS of 41 months versus 15 months; $p=0.01$). In a multivariate cox-regression analysis, the use of metformin was a statistically significant independent variable for DMFS and PFS ($p=0.02$ and 0.03).

Conclusion

Metformin use during cCRT is associated with an improved DMFS and PFS for locally advanced NSCLC patients, suggesting that metformin may be a valuable treatment addition in these patients. Evidently, our results merit to be verified in a prospective trial.

INTRODUCTION

Metformin is considered to be the medication of first choice for type II diabetes in multiple national and international guidelines ¹. It is a well-tolerated biguanide derivative that controls glycaemic levels and reduces the risk of diabetic complications. Apart from its effects in this metabolic disease, several population-based studies have reported that the use of metformin decreases the risk of developing cancer and improves cancer-related outcomes in diabetic patients ^{2,3}.

A postulated mechanism for this anti-cancer effect of metformin is the activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway and inhibition of the mammalian target of rapamycin (mTOR) signalling cascade ^{4,5}. Metformin also reduces circulating insulin levels, removing a possible growth stimulating factor for tumours expressing the insulin receptor ⁴. Finally, a preclinical study has demonstrated that metformin inhibits cellular oxygen consumption in the mitochondriae, thereby increasing the oxygen availability in hypoxic tumour regions. This tumour reoxygenation is expected to improve the radiation response ⁶.

Lung cancer is one of the most fatal cancers in the world, with most patients presenting with non-small cell lung cancer (NSCLC) ⁷. In patients diagnosed with locally advanced stage NSCLC, 5-year overall survival is poor (20%) despite intensive treatment with high dose radiotherapy, preferably combined with concurrent chemotherapy ⁸. The concomitant administration of chemotherapy has been shown to improve overall survival rates compared to sequential treatment (absolute benefit approximately 6% at 3 years), however, at the cost of an increased oesophageal toxicity ⁹. Advances in radiotherapy, e.g. shortening of overall treatment time and (isotoxic) dose escalation, have also resulted in improved local control and survival ¹⁰⁻¹². However, the benefit was generally modest and sometimes even absent: the high dose radiotherapy arm in the RTOG 0617 trial unexpectedly demonstrated an inferior outcome (albeit possibly by multifactorial cause) ¹³. This illustrates the need for new strategies to improve the effect of the current treatment modalities, preferably without increasing treatment-related toxicity.

The effect of metformin on lung cancer outcome has retrospectively been investigated in diabetic patients with stage II-IV NSCLC treated with first-line chemotherapy ¹⁴. The results indicate a better overall survival (OS) in patients treated with metformin *versus* those receiving insulin or other anti-diabetic drugs (median OS 20 *versus* 13 months, respectively; $p=0.003$). *In vitro* and *in vivo*, a synergistic effect of metformin has also been reported for NSCLC cell lines treated with any of the following: chemotherapy (cisplatin and etoposide), a tyrosine kinase inhibitor (gefitinib) and radiotherapy ^{5,15,16}.

The aim of this retrospective multicentre cohort study was to investigate whether the use of metformin during concurrent chemoradiotherapy (cCRT) for locally advanced NSCLC improved the treatment outcome for diabetic patients with respect to locoregional recurrence free survival, progression-free survival, distant metastasis free survival, and overall survival.

MATERIALS AND METHODS

Patients

We conducted a retrospective cohort study among patients treated in one of three participating departments of radiation oncology in the Netherlands: MAASTRO clinic (MC), Netherlands Cancer Institute (NCI) and the Amsterdam Medical Centre (AMC). All patients with biopsy proven locally advanced or medically inoperable NSCLC treated with concurrent chemoradiotherapy with curative intent between January 2008 and January 2013 were included in this study. The minimum applied radiation dose was set to be 50Gy (equivalent dose in 2-Gy fractions), administered in fractions of 1,5-2,75Gy once or twice daily ^{17,18}. The dose per fraction and total dose varied per institute and within institutes for patients included in a clinical trial investigating the effect of hyper- or hypofractionation (NCT01024829 and NCT00181545). The types of chemotherapy used were daily cisplatin 6mg/m² (NCI and AMC), or cisplatin 75mg/m² on day 1 (or carboplatin 5 mg.mL⁻¹.min⁻¹ of area under the concentration-time curve) and etoposide 100mg/m² on day 1-3 for 3 cycles every three weeks (MC). Some patients also participated in a phase I trial with escalated doses of vinorelbine (study details elsewhere) ¹⁹, others in a phase I-II study on the efficacy of combining daily dose cisplatin and concurrent radiotherapy with or without weekly cetuximab 250mg/kg ²⁰. All chemotherapeutic agents were administered concurrently. Patients treated with sequential chemoradiotherapy and patients with distant (oligo)metastases at the time of diagnosis were excluded. Data from MC and AMC were censored for analysis on November 1st, 2013, while the NCI data were censored on January 15th, 2013. Patients known to have used metformin during the course of radiotherapy were identified. The control group consisted of the remaining patients and included diabetic patients using anti-diabetic agents other than metformin. This study was approved by the Institutional Review Board of MC (LOKAAL 12-11-11/04-intern-6880) and registered at clinicaltrials.gov (NCT02109549).

Study outcomes

Initially, OS was selected as primary endpoint, as stated at clinicaltrials.gov. In hindsight, however, it was decided to change the primary endpoint to locoregional recurrence

free survival (LRFS) for diabetic patients are generally older and prone to have more comorbidities both influencing OS. Secondary endpoints were OS, progression-free survival (PFS), and distant metastasis free survival (DMFS). A locoregional recurrence was defined as tumour regrowth after previous tumour shrinkage or stable disease, or recurrence of tumour after a complete response, at the site of the primary tumour or in hilar, mediastinal or periclavicular lymph nodes. Recurrences were identified on repeated computed tomography (with or without Positron Emission Tomography) or chest x-ray. Pathologic confirmation of recurrent disease was not compulsory. Progression-free survival was calculated from the first day of radiation treatment until distant or locoregional progression occurred or until study censoring at the date of last follow-up or death. For the patients irradiated at MC and the AMC, the occurrence of a second event (local recurrence or distant metastases) after first progression was also recorded and incorporated in the analyses for LRFS and DMFS. Outcome for LRFS, PFS and DMFS was censored at the first event for the NCI patients. Overall survival data were collected from a national database and therefore known for all but one patient. Death was not considered a competing risk for LRFS, PFS and DMFS since patients were censored at the date of last follow-up. In case of an unknown outcome, patients were excluded from the analysis for that specific endpoint.

Statistical analysis

All statistics were performed using IBM SPSS (v.22). Baseline patient characteristics for metformin users and non-users were compared using a Pearson's chi-square test for categorical variables and a Student's t-test for continuous variables. The Kaplan-Meier method was used to obtain actuarial survival curves for LRFS, OS, PFS, and DMFS. Log-rank tests were performed to compare outcomes. After univariate analysis, the influence of well-known prognostic factors such as age, gender, WHO performance status (WHO PS) and disease stage on outcome was evaluated in a multivariate analysis alongside metformin use, using stepwise backwards cox regression. All statistical tests were two tailed and a p-value of <0.05 was considered significant.

RESULTS

After exclusion of the patients not meeting the inclusion criteria, 682 patients were eligible for analysis. A total of 281 patients (41 %) were treated at MC, 323 patients at the NCI (47%) and 78 at the AMC (11%). Fifty-nine patients used metformin during their radiation treatment and were allocated to the case cohort, whereas the remaining patients (n=623) formed the control group. The baseline patient characteristics are shown in Table 1. The cohort consisted of 426 males (63%), the median age at diagnosis was 63

Table 1: Patient characteristics.

	All patients		Metformin		No Metformin		p value
	N	%	N	%	N	%	
Number of patients							0.03
Total	682	100.0	59	8.7	623	91.3	
Maastricht Clinic	281	41.2	20	33.9	261	41.9	
NCI	323	47.4	26	44.1	297	47.7	
AMC	78	11.4	13	22.0	65	10.4	
Age (mean, yrs)	63	(29-87)	69	(48-84)	62	(29-87)	<0.001
FU (median, mo)	30	(1-65)	21	(3-64)	30	(1-65)	0.40
Gender							0.40
Male	426	62.5	40	67.8	386	62.0	
Female	256	37.5	19	32.2	237	38.0	
WHO PS							0.38
0	210	30.8	16	27.1	194	31.1	
1	408	59.8	34	57.6	374	60.0	
2	52	7.6	8	13.6	44	7.1	
3	7	1.0	1	1.7	6	1.0	
4	1	0.1	0	0.0	1	0.2	
Unknown	4	0.6	0	0.0	4	0.6	
T stage							0.39
T0	17	2.5	3	5.1	14	2.2	
T1	86	12.6	10	16.9	76	12.2	
T2	194	28.5	16	27.1	178	28.5	
T3	141	20.7	14	23.7	127	20.4	
T4	237	34.8	16	27.1	221	35.5	
Unknown	7	1.0	0	0.0	7	1.1	
N stage							0.95
N0	92	13.5	8	13.6	84	13.5	
N1	48	7.0	3	5.1	45	7.2	
N2	390	57.2	35	59.3	355	57.0	
N3	150	22.0	13	22.0	137	22.0	
Unknown	2	0.3	0	0.0	2	0.3	
Overall stage							0.37
II	38	5.6	5	8.5	33	5.3	
III	644	94.4	54	91.5	590	94.7	
Histology							0.71
SCC	228	33.4	22	37.3	206	33.1	
ACC	166	24.3	12	20.3	154	24.7	
NSCLC NOS*	288	42.3	25	42.4	263	42.2	
GTV volume (mean)*	122.6cm ³	(0.17-1823)	122.6cm ³	(3.3-429)	122.6cm ³	(0.17-1823)	1.00
Total dose (mean)	66.1Gy	(50-129.6)	65.6Gy	(55-72.2)	66.2Gy	(50-129.6)	0.43
N fractions (mean)	30.8	(19-45)	29.2	(20-42)	30.2	(19-45)	0.37
Fraction dose (mean)	2.3Gy	(1.2-5.4)	2.4Gy	(1.6-3.0)	2.3Gy	(1.2-5.4)	0.58

NCI, Netherlands Cancer Institute; AMC, Amsterdam Medical Center; FU, follow-up; WHO PS, World Health Organization Performance Score; SCC, squamous cell carcinoma; ACC, adenocarcinoma; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; GTV, Gross Tumour Volume

years (range 29-87 years), and most patients were in good general condition (90% WHO PS 0-1). The patients using metformin were on average 7 years older than the patients in the control group ($p<0.001$). All the included patients had a proven NSCLC, with the majority classified as squamous cell carcinoma (33%) or adenocarcinoma (24%), and most patients had stage III disease (94%). At diagnosis, nodal involvement was present in 86% of the included patients. No other significant differences between the control group and the metformin users were observed with respect to tumour size and stage, WHO score, gender, histology, or administered radiation dose. The mean total dose delivered was 66.1 Gy (range 50 – 129.6 Gy) in mean 31 fractions (range 19 – 45) of 2.3 Gy (mean dose, range 1.2 – 5.4 Gy)^{17,18}. The highest administered dose was 129.6 Gy, for a patient participating in the PET boost study (NCT01024829)²¹. Table 2 shows the comparison of outcome parameters between metformin and non-metformin users. For LRFS, the median follow-up was 18 months (range 0-64 months). A total of 210 patients developed a locoregional recurrence (31%), 14 of these patients were metformin users (24%) and 196 control patients (31%). The median overall LRFS for the control group was 44 months, whereas this was not reached for the metformin group ($p=0.15$, Figure 1A).

Table 2: Comparison of outcome parameters between metformin- and non-metformin-users.

	All patients (n=682)	Metformin (n=59)	No Metformin (n=623)	p value
OS				0.39
Deaths (%)	51	44.1	51.7	
2yr (%)	49.8	62.4	49.0	
Median (mo)	24	33	23	
LRFS				0.15
LR recurrence (%)	30.8	23.7	31.5	
2yr (%)	60.8	72.0	59.7	
Median (mo)	44	NR	44	
DMFS				0.01
Distant metastases (%)	38.3	22	39.8	
2yr (%)	55.1	74.4	53.3	
Median (mo)	36	NR	36	
PFS				0.01
Progression (%)	54.4	39	55.9	
2yr (%)	39	57.9	37.3	
Median (mo)	15	41	15	

OS, overall survival; LRFS, locoregional recurrence free survival; LR, locoregional; DMFS, distant metastasis free survival; PFS, progression free survival

Figure 1: Kaplan–Meier survival curves for metformin users vs non-metformin users, (A) locoregional recurrence free survival, (B) overall survival, (C) distant metastasis free survival, (D) progression-free survival.

The median follow-up for OS was 30 months (range 1-65 months). By the end of the follow-up period, 348 of the 682 patients had died (51%), 26 patients in the metformin group (44%) and 322 patients in the control group (52%). The median OS was 24 months, 33 months for the metformin users and 23 months in the control group ($p=0.39$, Figure 1B). The 2 year OS was 62% *versus* 49% for the metformin and control group, respectively. Overall, survival was worse for men with a median overall survival of 22 months *versus* 30 months for women ($p=0.001$).

Distant metastases occurred in 261 patients (38%) after a median follow up of 19 months (range 0-64 months). The 2-year DMFS was significantly better for the metformin group (74% *versus* 53%; $p=0.01$, Figure 1C), as well as the PFS (58% *versus* 37%; $p=0.01$, Figure 1D). Median PFS was 41 months for metformin users *versus* 15 months in the control group.

A multivariate cox-regression analysis was performed to evaluate the influence of several variables on the LRFS, OS, DMFS and PFS (Table 3). Gender and WHO PS were variables significantly associated with overall survival ($p=0.001$ and $p=0.005$). For DMFS and PFS, the use of metformin was a statistically significant independent variable ($p=0.02$ and $p=0.03$, respectively).

Table 3: Backwards Cox-regression multivariate analysis, full model*.

	LRFS			OS			DMFS			PFS		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Metformin use¹	0.71	0.41-1.23	0.22	0.86	0.57-1.28	0.45	0.52	0.30-0.91	0.02	0.63	0.41-0.96	0.03
Age²	1.00	0.99-1.02	0.64	1.01	1.00-1.02	0.08	0.99	0.98-1.00	0.05	1.00	0.99-1.01	0.48
Gender¹	1.23	0.95-1.68	0.10	1.50	1.19-1.89	0.001	0.92	0.71-1.18	0.50	1.10	0.89-1.37	0.37
Stage III¹	0.95	0.52-1.75	0.87	0.90	0.57-1.43	0.66	1.26	0.68-2.32	0.45	1.21	0.74-1.98	0.44
WHO-PS 2-3¹	0.86	0.44-1.67	0.65	1.87	1.20-2.89	0.005	1.53	0.91-2.57	0.11	1.33	0.85-2.07	0.21

LRFS = locoregional recurrence free survival, NS = not significant, OS = overall survival, DMFS = distant metastasis free survival, PFS = progression free survival

* For ultimately significant variables ($p < 0.05$), the HRs, 95% CIs and P values are printed in bold. For non-significant variables, the outcomes reflect the values at the moment of exclusion from backwards regression (metformin use was always included in the model).

1: categorical variable (reference category WHO-PS 0-1 for WHO-PS; Female for Gender; Stage II for Stage and No metformin for Metformin use)

2: continuous variable: Age in years

DISCUSSION

A significant increase in progression free survival and distant metastasis free survival was found for NSCLC patients treated with cCRT while using metformin for diabetes. This outcome was observed despite the underpowered nature of this study, due to a relatively small number of metformin users and a modest follow up period. After multivariate analysis, metformin was found to be a significant factor for both DMFS and PFS. The primary endpoint, LRFS, was not statistically significantly superior for the metformin users, but taking the power of the analysis into account, the effect is of sufficient size (HR 0.71; 95% CI 0.41-1.23; $p = 0.22$) to warrant further investigation.

Metformin has previously been reported to improve outcomes in several other solid cancer types, e.g., prostate, colorectal, breast, oesophagus, and for NSCLC the first reports have been published as well^{3,14,22-29}. Lin *et al.*²² and Tan *et al.*¹⁴ both investigated the effect of adding metformin to chemotherapy for stage IV NSCLC and observed an improved OS for patients using metformin. Besides the current study, the only study performed in locally advanced NSCLC patients is the retrospective cohort study by Ahmed *et al.*²³, including 166 patients treated with cCRT, of which 20 used metformin during treatment. After a median follow-up of 17 months, the authors did not observe a difference in OS, PFS, LRFS for the diabetic NSCLC patients on metformin compared with the non-diabetic patients or the diabetic patients on other anti-diabetic drugs. However, it is unlikely to find a significant difference in outcome considering the small patient cohort and short patient follow up. The cohort we investigated was considerably larger,

and, conversely, we observed a significantly improved PFS and DMFS for the diabetic patients on metformin.

This improved outcome may either reflect a direct inhibitory effect of metformin on tumour cell growth and development of distant metastases, or the manifestation of sensitisation to the chemo- and/or radiotherapy. For NSCLC, the direct antineoplastic effect of metformin has previously been described in a number of (pre)clinical studies with several studies showing a growth inhibition of lung cancer cells *in vitro* and *in vivo* ^{5,15,30,31}. The underlying mechanism is not entirely understood, but is to a certain extent associated with AMPK activation and reduced mTOR signalling ^{4,5}. Metformin is known to ameliorate glycaemic control through liver kinase B1 and AMPK mediated inhibition of hepatic gluconeogenesis, and stimulation of glucose uptake in skeletal muscles. The insulin sensitivity of peripheral tissues increases, and the fasting blood glucose and circulating insulin levels both decrease ^{4,32}. This indirect, insulin-lowering effect is hypothesised to be partly responsible for the anticancer effect of metformin ⁴; hyperinsulinemia has been shown to have a tumour cell growth promoting effect in several cancer types, including lung cancer ^{33,34}. An *in vivo* analysis in mice performed by Algire *et al.* ³⁵ showed that metformin can counteract the negative effects of insulin on the growth of lung tumour cells. Moreover, metformin also inhibits the mTOR signalling cascade in cancer cells through activation of AMPK, resulting in a decrease in both protein synthesis and cell proliferation (insulin-independent effect) ^{4,36,37}. In a preclinical study, Storozhuk *et al.* ⁵ showed that metformin sensitises NSCLC cells to ionising radiation, leading to an increased radiation response. Metformin has been shown to reduce oxygen consumption *in vitro* and *in vivo* in multiple cancer cell lines ⁶. Combining these observations and considering radioresistance of hypoxic tumours, the observed tumour reoxygenation may be a plausible radiobiological explanation for the radiosensitising effect of metformin ³⁸. The hypothesised mechanism of action of metformin on tumour cell proliferation and radiation response is summarised in Figure 2.

Furthermore, metformin has been reported to improve responses to chemotherapy or targeted agents in several (pre)clinical studies on NSCLC ^{15,16,39,40}. In a phase II clinical trial with sorafenib monotherapy for 57 pre-treated Stage IIIB-IV NSCLC patients with a KRAS mutation, a partial response occurred more frequently in the five patients using metformin during treatment compared with the non-users ($p=0.01$) ⁴¹. Groenendijk *et al.* ⁴² recently published a *post hoc* analysis on that study, reporting that six weeks after treatment with sorafenib, all patients using metformin had either a partial response or stable disease, while 27 of the patients not using metformin had progressive disease ($p=0.01$). Taking these findings from bed to benchside, the authors treated NSCLC cell lines and mouse NSCLC-xenograft tumours with sorafenib and metformin (monotherapy or in

Figure 2: Hypothesised mechanism of action of metformin use on tumour cell growth and radiation response.

combination) and found an anti-proliferative effect in the NSCLC cell lines and a lower mean tumour volume in the xenografts treated with the drug combination compared to sorafenib monotherapy ($p=0.046$).

Most of the published clinical studies on the effects of metformin are observational and retrospective, resulting in several statistical limitations and a high risk of confounding factors⁴³. We corrected our results for several well-known prognostic factors such as age, WHO PS and stage in a multivariate analysis. This did not influence our results. However, when correcting for treatment centre, one of the centres showed a slightly better outcome. Most likely, this difference stems from local variation in selection criteria for cCRT (data available in additional table). Due to the retrospective nature of the current study, residual confounding cannot be excluded. First, the positive effect of metformin on PFS and DMFS may reflect a biologically less aggressive NSCLC in diabetic patients who happen to be using metformin. Second, the relatively small group of metformin users in the cohort (8.4%), their significantly older age and relatively short follow up may have influenced our results and possibly explain the lack of difference in OS rate. Third, the severity and duration of diabetes, the insulin levels during treatment, the duration of metformin use, and other (antidiabetic) co-medications were not taken into account. Fourth, even though the concurrent chemotherapy regimens were heterogeneous and

influenced our results, it was impossible to take the type and dose of chemotherapy and/or targeted therapy into account. However, the optimal regimen for NSCLC is a general point of discussion; good quality, evidence based comparisons are lacking⁴⁴.

Noteworthy, the conclusions of this study should be interpreted with caution for the reasons mentioned earlier. Furthermore, unanswered questions include an interaction of metformin with chemotherapy and/or radiotherapy or neither, and the effect of metformin use in non-diabetic patients suffering from NSCLC. A phase II clinical trial addressing the latter question in non-diabetic patients with locally advanced NSCLC undergoing chemoradiotherapy with administration of metformin is planned by the Ontario Clinical Oncology Group (OCOG, NCT02115464).

CONCLUSION

In conclusion, we observed a significantly improved DMFS and PFS for locally advanced diabetic NSCLC patients treated with metformin during concurrent chemoradiotherapy. This finding combined with the growing body of (pre)clinical evidence on the effectiveness of metformin for NSCLC justifies prospective trials adding metformin to settled treatments as an anti-cancer agent.

Additional table: Backwards Cox-regression multivariate analysis.

	LRFS			OS			DMFS			PFS		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Center B¹	0.89	0.67-1.18	0.42	1.08	0.87-1.35	0.49	0.79	0.61-1.01	0.06	0.92	0.75-1.14	0.45
Center C¹	0.58	0.34-0.98	0.04	0.53	0.33-0.85	0.008	0.49	0.30-0.80	0.005	0.60	0.40-0.88	0.01

LRFS = local recurrence free survival, OS = overall survival, DMFS = distant metastasis free survival, PFS = progression free survival

1: categorical variable (reference category treatment center A)

REFERENCES

1. International Diabetes Federation Guideline Development G. Global guideline for type 2 diabetes. *Diabetes research and clinical practice*. 2014;104(1):1-52.
2. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(25):3069-3075.
3. Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. *European urology*. 2013;63(4):709-716.
4. Dowling RJ, Goodwin PJ, Stambolic V. Understanding the benefit of metformin use in cancer treatment. *BMC medicine*. 2011;9:33.
5. Storozhuk Y, Hopmans SN, Sanli T, et al. Metformin inhibits growth and enhances radiation response of non-small cell lung cancer (NSCLC) through ATM and AMPK. *British journal of cancer*. 2013;108(10):2021-2032.
6. Zannella VE, Dal Pra A, Muaddi H, et al. Reprogramming metabolism with metformin improves tumor oxygenation and radiotherapy response. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2013;19(24):6741-6750.
7. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: a cancer journal for clinicians*. 2011;61(2):69-90.
8. Harris JP, Murphy JD, Hanlon AL, Le QT, Loo BW, Jr., Diehn M. A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer. *International journal of radiation oncology, biology, physics*. 2014;88(4):872-884.
9. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2006;17(3):473-483.
10. Bayman N, Blackhall F, McCloskey P, Taylor P, Faivre-Finn C. How can we optimise concurrent chemoradiotherapy for inoperable stage III non-small cell lung cancer? *Lung cancer*. 2014;83(2):117-125.
11. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 1999;52(2):137-148.
12. Mauguén A, Le Pechoux C, Saunders M, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30(22):2788-2797.
13. Bradley JD, Paulus R, Komaki R, 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. *The Lancet Oncology*. 2015;16(2):187-199.
14. Tan BX, Yao WX, Ge J, et al. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. *Cancer*. 2011;117(22):5103-5111.

15. Teixeira SF, Guimaraes Idos S, Madeira KP, Daltoe RD, Silva IV, Rangel LB. Metformin synergistically enhances antiproliferative effects of cisplatin and etoposide in NCI-H460 human lung cancer cells. *Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia*. 2013;39(6):644-649.
16. Morgillo F, Sasso FC, Della Corte CM, et al. Synergistic effects of metformin treatment in combination with gefitinib, a selective EGFR tyrosine kinase inhibitor, in LKB1 wild-type NSCLC cell lines. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2013;19(13):3508-3519.
17. van Baardwijk A, Wanders S, Boersma L, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(8):1380-1386.
18. 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. *European journal of cancer*. 2000;36(5):592-600.
19. Dingemans AM, Bootsma G, van Baardwijk A, et al. A phase I study of concurrent individualized, isotoxic accelerated radiotherapy and cisplatin-vinorelbine-cetuximab in patients with stage III non-small-cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2014;9(5):710-716.
20. van den Heuvel MM, Uytendinck W, Vincent AD, et al. Additional weekly Cetuximab to concurrent chemoradiotherapy in locally advanced non-small cell lung carcinoma: efficacy and safety outcomes of a randomized, multi-center phase II study investigating. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2014;110(1):126-131.
21. van Elmpt W, De Ruyscher D, van der Salm A, et al. The PET-boost randomised phase II dose-escalation trial in non-small cell lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;104(1):67-71.
22. Lin JJ, Gallagher EJ, Sigel K, et al. Survival of patients with stage IV lung cancer with diabetes treated with metformin. *American journal of respiratory and critical care medicine*. 2015;191(4):448-454.
23. Ahmed I, Ferro A, Cohler A, et al. Impact of metformin use on survival in locally-advanced, inoperable non-small cell lung cancer treated with definitive chemoradiation. *Journal of thoracic disease*. 2015;7(3):346-355.
24. Yu H, Yin L, Jiang X, et al. Effect of metformin on cancer risk and treatment outcome of prostate cancer: a meta-analysis of epidemiological observational studies. *PloS one*. 2014;9(12):e116327.
25. Skinner HD, Crane CH, Garrett CR, et al. Metformin use and improved response to therapy in rectal cancer. *Cancer medicine*. 2013;2(1):99-107.
26. Zhang ZJ, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. *Diabetes, obesity & metabolism*. 2014;16(8):707-710.
27. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(20):3297-3302.
28. Goodwin PJ, Ligibel JA, Stambolic V. Metformin in breast cancer: time for action. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2009;27(20):3271-3273.
29. Skinner HD, McCurdy MR, Echeverria AE, et al. Metformin use and improved response to therapy in esophageal adenocarcinoma. *Acta oncologica*. 2013;52(5):1002-1009.

30. Izzotti A, Balansky R, D'Agostini F, et al. Modulation by metformin of molecular and histopathological alterations in the lung of cigarette smoke-exposed mice. *Cancer medicine*. 2014.
31. Muaddi H, Chowdhury S, Vellanki R, Zamiara P, Koritzinsky M. Contributions of AMPK and p53 dependent signaling to radiation response in the presence of metformin. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2013;108(3):446-450.
32. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? *Diabetologia*. 2013;56(9):1898-1906.
33. Frasca F, Pandini G, Sciacca L, et al. The role of insulin receptors and IGF-I receptors in cancer and other diseases. *Archives of physiology and biochemistry*. 2008;114(1):23-37.
34. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Annals of the New York Academy of Sciences*. 2011;1243:54-68.
35. Algire C, Zakikhani M, Blouin MJ, Shuai JH, Pollak M. Metformin attenuates the stimulatory effect of a high-energy diet on in vivo LLC1 carcinoma growth. *Endocrine-related cancer*. 2008;15(3):833-839.
36. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Molecular cancer therapeutics*. 2010;9(5):1092-1099.
37. Petroulakis E, Mamane Y, Le Bacquer O, Shahbazian D, Sonenberg N. mTOR signaling: implications for cancer and anticancer therapy. *British journal of cancer*. 2006;94(2):195-199.
38. Li L, Hu M, Zhu H, Zhao W, Yang G, Yu J. Comparison of 18F-Fluoroerythronitroimidazole and 18F-fluorodeoxyglucose positron emission tomography and prognostic value in locally advanced non-small-cell lung cancer. *Clinical lung cancer*. 2010;11(5):335-340.
39. Iliopoulos D, Hirsch HA, Struhl K. Metformin decreases the dose of chemotherapy for prolonging tumor remission in mouse xenografts involving multiple cancer cell types. *Cancer research*. 2011;71(9):3196-3201.
40. Rocha GZ, Dias MM, Ropelle ER, et al. Metformin amplifies chemotherapy-induced AMPK activation and antitumoral growth. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2011;17(12):3993-4005.
41. Dingemans AM, Mellema WW, Groen HJ, et al. A phase II study of sorafenib in patients with platinum-pretreated, advanced (Stage IIIB or IV) non-small cell lung cancer with a KRAS mutation. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2013;19(3):743-751.
42. Groenendijk FH, Mellema WW, van der Burg E, et al. Sorafenib synergizes with metformin in NSCLC through AMPK pathway activation. *International journal of cancer Journal international du cancer*. 2015;136(6):1434-1444.
43. Zanders MM, Vissers PA, van de Poll-Franse LV. Association between metformin use and mortality in patients with prostate cancer: explained by confounding by indication? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2014;32(7):701.
44. Addeo A, Comins C. Optimal Concurrent Chemoradiotherapy Regimen in Non-Small-Cell Lung Cancer: Prospective, Randomized Data Still Required. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015;33(26):2928.

CHAPTER 5

Particle therapy for non-small cell lung tumours: where do we stand?

A systematic review of the literature

Krista C.J. Wink, Erik Roelofs, Timothy Solberg, Liyong Lin, Charles B. Simone II,
Annika Jakobi, Christian Richter, Philippe Lambin, Esther G.C. Troost

Frontiers in Oncology 2014; 4: 292

ABSTRACT

This review article provides a systematic overview of the currently available evidence on the clinical effectiveness of particle therapy for the treatment of non-small cell lung cancer and summarises findings of *in silico* comparative planning studies. Furthermore, technical issues and dosimetric uncertainties with respect to thoracic particle therapy are discussed.

INTRODUCTION

Over the last decades, improvements in surgical techniques and (chemo)radiotherapy have increased the survival rate in patients with lung cancer¹. Despite this, the survival of patients with locally advanced non-small cell lung cancer (NSCLC) remains poor, with a five year overall survival of 15% for stage III NSCLC patients treated with concurrent chemoradiotherapy².

Prior studies have suggested a higher tumour dose can result in increased locoregional control, and consequently in an improved disease-specific survival^{3,4}. Different strategies to escalate the dose to the primary target volume have been studied, *i.e.*, isotoxic dose enhancement, hyperfractionation, or dose-rescaling on an individual basis⁵⁻⁷. However, the tumour-surrounding healthy tissues (healthy lung, heart, mediastinal vessels, spinal cord and brachial plexus) are often dose limiting.

Even though modern radiotherapy techniques (*e.g.*, 3D conformal radiotherapy; 3D-CRT, or Intensity Modulated Radiation Therapy; IMRT) decrease dose to surrounding tissues compared with 2D techniques, particle beam therapy may offer an even greater advantage. The favourable properties of charged particles in terms of dose distribution and radiobiological effectiveness make it an option worth investigating for the treatment of NSCLC. Treatment with protons or carbon ions can enable dose escalation beyond what can be achieved with the different photon techniques⁸. There are, however, several difficulties with the delivery of particle beams to a tumour in the lung. These include the fact that the tumour and other anatomy may be moving, that variations exist in the water equivalent thickness of the beam path, and that the range uncertainties associated with pencil beam scanning (PBS) techniques are particularly sensitive to motion and setup errors^{9,10}.

The aim of this article is to systematically review the currently available evidence on the clinical effectiveness and *in silico* comparative planning studies of particle therapy for the treatment of NSCLC. The technical issues and dosimetric uncertainties with respect to thoracic particle therapy are also discussed.

METHODS

The PubMed database was searched by two researchers to identify studies about particle therapy for NSCLC. Search items were: *lung, proton, particle, hadron, carbon, cancer, tumour, neoplasm, therapy, treatment, radiation therapy, radiotherapy, irradiation*, and *NSCLC*. The search terms were used in different combinations and plural forms and the search was limited to articles in English. References were screened for additional articles.

Three types of studies were included: studies reporting on the outcomes of particle therapy for NSCLC, studies comparing dose distributions in (*in silico*) planning studies, and studies reporting on technical issues with particle therapy for NSCLC.

RESULTS

Clinical outcome

All the studies reporting on clinical outcome of particle therapy for NSCLC were published by one of the following centres treating NSCLC patients with particle beams: the Loma Linda University Medical Center (LLUMC, Loma Linda, California, USA), the MD Anderson Cancer Center (MDACC, Houston, Texas, USA), the Proton Medical Research Center (PMRC, Tsukuba, Japan), the Hyogo Ion Beam Medical Center (HIBMC, Tatsuno, Japan), and the National Cancer Center Hospital East (NCCHE, Chiba, Japan). Due to overlapping study periods from the same institutions reporting on the same disease stages, it is reasonable to assume that the same patients were analysed in multiple reports. This was, however, not always obvious because follow-up periods and patient numbers differed. Therefore, it was decided to include all the published studies in this review. In instances where the studied patient cohort was identical (same number of patients, patient characteristics, and follow-up period), only the most recent study reporting on clinical outcome was selected. Study characteristics are summarised in Table 1 (early stage NSCLC) and Table 2 (advanced stage NSCLC).

Early stage NSCLC

Study descriptions

Fourteen studies investigated particle therapy for early stage (stage I or II) NSCLC. The patients included were either medically inoperable or refused surgery, since surgery is still regarded as the first choice for treatment of Stage I NSCLC¹¹⁻¹³. Six studies reported the outcome of patients treated with protons only¹⁴⁻¹⁹, four used carbon ions only²⁰⁻²³, two studies reported outcome for both carbon ions and protons^{24,25}, and two studies treated patients with a combination of photons and protons^{26,27}. The most recent study is that of Kanemoto *et al*¹⁹. The researchers retrospectively evaluated disease control rates after high dose proton beam therapy (PBT) in 74 patients with stage I NSCLC, with tumour doses of 66 Gy-equivalent (GyE) in 10-12 fractions for peripheral tumours (74% of all tumours) and 72.6 GyE in 22 fractions for centrally located tumours. Another retrospective study from the same centre (with different investigators), evaluated the outcome of PBT for 55 medically inoperable patients with stage I NSCLC, using the same total dose and fractionation¹⁷. The study periods of both studies overlap, making it reasonable to assume that the patients included in the study by Nakayama *et al*¹⁷ were also assessed by the Kanemoto group¹⁹.

Table 1: Study descriptions early stage NSCLC.

Study (characteristics); location	Beam, energy, technique	Chemotherapy	Fractionation schedule, TTD/no. of fractions/OTT	Patient selection criteria/risk factors	Stage distribution
PROTON BEAM ONLY					
Bush <i>et al.</i> ²⁶ (prospective, n=37); USA, Loma Linda	Proton; Photon + proton PSc	No	PBT 51 GyE/10 fr/2 weeks; photons, 45 Gy/25 fr + protons, 28.8 GyE/16 fr/5 weeks	NSCLC stage I-IIIa; medically inoperable/refused surgery	Stage I, 27; Stage II, 2; Stage IIIa, 8
Shioyama <i>et al.</i> ²⁷ (retrospective, n=51); Japan, Tsukuba	Proton, 250MeV, PSc (n=33); Photon + proton (n=18)	6 patients prior chemotherapy (all advanced stages)	Median 76 Gy (range 49-93 Gy), median fr dose 3.0 Gy (range 2-6 Gy), median OTT 43 days	NSCLC, medically inoperable/refused surgery	Stage IA/IB, 9/19; Stage IIA/IIIB, 3/6; Stage IIIA/IIIB, 8; Stage IV, 1, recurrent disease, 5.
Bush <i>et al.</i> ¹⁴ (Phase II, n=68); USA, Loma Linda	Proton, PSc	No	51 GyE/10 fr/2 weeks (n=22); 60 GyE/10 fr/2 weeks (n=46)	NSCLC stage I, medically inoperable n=63/refused surgery (n=5)	Stage IA, 29; Stage IB, 39
Nihei <i>et al.</i> ¹⁵ (retrospective, n=37); Japan, Chiba	Proton, 150 or 190 MeV, PSc	No	70 GyE/20 fr/4-5 weeks (n = 3); 80 GyE/20 fr/4-5 weeks (n = 17); 88 GyE/20 fr/4-5 weeks (n = 16); 94 GyE/20 fr/4-5 weeks (n = 1)	NSCLC stage I; medically inoperable (n=23)/ refused surgery (n=14), tumour size ≤ 5cm, pO ₂ ≥ 60 torr, Zubrad PS 0-2	Stage IA, 17; Stage IB, 20
Hata <i>et al.</i> ¹⁶ (prospective, n=21), Japan, Tsukuba	Proton, 155-200 MeV, PSc	No	50 Gy/10 fr/2 weeks (n=3); 60 Gy/10 fr/2 weeks (n=18)	NSCLC stage I, medically inoperable (n=9)/refused surgery (n=12), ECOG PS 0-2, no previous RT or chemotherapy for NSCLC	Stage IA, 11; Stage IB 10
Nakayama <i>et al.</i> ¹⁷ (retrospective, n=55) (58 tumours) Japan, Tsukuba	Proton, 155 – 250 MeV, PSc	No	Peripheral tumours 66 GyE/10 fr/2 weeks (n=41), central tumours 72.6 GyE/22 fr/4.5 weeks (n=17)	NSCLC stage I; EORTC PS 0-2, medically inoperable (n=52)/ refused surgery (n=3), Exclusion: pleural effusion, tumour close to stomach/oesophagus	Stage IA, 30; Stage IB, 28

Table 1: Study descriptions early stage NSCLC. (continued)

Study (characteristics); location	Beam, energy, technique	Chemotherapy	Fractionation schedule, TTD/no. of fractions/OTT	Patient selection criteria/risk factors	Stage distribution
Bush <i>et al.</i> ¹⁸ (phase 2, n=11); USA, Loma Linda	Proton, PSc	No	Dose escalation during study, 51 GyE/10 fr/2 weeks (n=29), 60 GyE/10 fr/2 weeks (n=56), 70 GyE/10 fr/2 weeks (n=26)	NSCLC stage I, medically inoperable/refused surgery	Stage IA, 47; Stage IB, 64
Kanemoto <i>et al.</i> ¹⁹ (retrospective, n=74, 80 tumours), Japan, Tsukuba	Proton, 155 – 250 MeV, PSc	No	Peripheral tumours 66 GyE/10-12 fr/2-2.5 weeks (n=59), central tumours 72.6 GyE/22 fr/4.5 weeks (n=21)	NSCLC stage I	Stage IA, 59; Stage IB, 21
C-ION (COMBINED WITH PROTON BEAM)					
Iwata <i>et al.</i> ²⁴ (retrospective, n=80), Japan, Hyogo	Proton 150 MeV, PSc; C-ion 320 MeV, PSc	No	Proton: 80 GyE/20 fr/4 weeks (n=20), 60 GyE/10 fr/2 weeks (n=37), C-ion: 52.8 GyE/4 fr/1 week (n=23)	NSCLC stage I, medically inoperable (n=47)/refused surgery (n=43), WHO PS 0-2, no history lung cancer or previous chest RT /chemo	Stage IA, 42; Stage IB, 38
Iwata <i>et al.</i> ²⁵ (retrospective, (partially subgroup of cohort Iwata 2010), n=70), Japan, Hyogo	Proton 150 MeV, PSc; C-ion 320 MeV, PSc	No	Proton: 80 GyE/20 fr/4 weeks (n=14), 60 GyE/10 fr/2 weeks (n=20), 66 GyE/10 fr/2 weeks (n=8), 70.2 GyE/26 fr/5.5 weeks (n=1). C-ion: 52.8 GyE/4 fr/1 week (n=16), 66 GyE/10 fr/2 weeks (n=8), 68.4 Gye/9 fr/2 weeks (n=3)	NSCLC cT2a/T2bN0M0, medically inoperable (n=40)/refused surgery (n=30), WHO PS 0-2, no history lung cancer or previous chest RT/chemotherapy	Stage IB, 47; Stage IIA, 23.
Miyamoto <i>et al.</i> ²⁰ (phase I/II, n=81, 82 tumours), Japan, Chiba	C-ion, 290-350-400 MeV, PSc	No	59.4-95.4 GyE/18 fr/6 weeks (n=48), 68.4-79.2 GyE/9 fr/3 weeks (n=34)	Inoperable NSCLC stage I, WHO PS 0-2, no history of RT to target, no prior chemotherapy <4 weeks	Stage IA, 41; Stage IB, 41

Table 1: Study descriptions early stage NSCLC. (continued)

Study (characteristics); location	Beam, energy, technique	Chemotherapy	Fractionation schedule, TTD/no. of fractions/OTT	Patient selection criteria/risk factors	Stage distribution
Miyamoto <i>et al.</i> ²¹ (phase II, n=79), Japan, Chiba	C-ion, 290-350-400 MeV, PSc	No	52.8 GyE/4 fr/1 week (IA) 60 GyE/4 fr/1 week (IB)	NSCLC stage I, medically inoperable/refused surgery, WHO PS 0-2, no history of RT to target, no prior chemotherapy <4 weeks	Stage IA, 42; Stage IB, 37.
Miyamoto <i>et al.</i> ²² (phase II, n=50, 51 tumours), Japan, Chiba	C-ion, 290-350-400 MeV, PSc	No	72 GyE/9 fr/3 weeks	Peripheral NSCLC stage I, WHO PS 0-2, no history of RT to target, no prior chemotherapy <4 weeks	Stage IA, 30; Stage IB, 21
Sugane <i>et al.</i> ²³ (phase II, n=28, 29 tumours), Japan, Chiba	C-ion, 290-350-400 MeV, PSc	No	72.0 GyE/9 fr/3 weeks (all, 1999-2000, n=12), 60.0 GyE/4 fr/1 week (IA, n=11), 52.8 GyE/4 fr/1 week (IB, n=6)	NSCLC stage I; elderly, aged ≥ 80 years	Stage IA, 12; Stage IB, 17.

ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; fr, fraction(s); OTT, overall treatment time; PS, performance score; PSc, passive scattering; RT, radiotherapy; TTD, total tumour dose; USA, United States of America; WHO, World Health Organization.

Table 2: Study descriptions advanced stage NSCLC.

Study (characteristics); location	Beam, energy, technique	Chemotherapy	Fractionation schedule, TTD/ no. of fractions/OTT	Patient selection criteria/risk factors	Stage distribution
PROTON BEAM ONLY					
Bush <i>et al.</i> ²⁶ (prospective, n=37); USA, Loma Linda	Proton; Photon + proton PSc	No	51 GyE/10 fr/2 weeks; photons, 45 Gy/25 fr + protons, 28.8 GyE/16 fr/5 weeks	NSCLC stage I-IIIa; medically inoperable/refused surgery	Stage I, 27; Stage II, 2; Stage IIIa, 8
Shioyama <i>et al.</i> ²⁷ (retrospective, n=51); Japan, Tsukuba	Proton, 250MeV, PSc (n=33); Photon + proton (n=18)	6 patients prior chemotherapy (all advanced stages)	Median TD 76 Gy (range 49-93 Gy), median fr dose 3.0 Gy (range 2-6 Gy), median OTT 43 days	NSCLC, medically inoperable/refused surgery	Stage IA/IB, 9/19; Stage IIA/IIIB, 3/6; Stage IIIA/IIIB, 8; Stage IV, 1, recurrent disease, 5.
Chang <i>et al.</i> ³² (phase II, n=44), USA, Houston	Proton, PSc	Concurrent, weekly carboplatin (2AUC) + paclitaxel (50mg/m ²) (n=44). (neo)Adjuvant chemotherapy allowed (n=19)	74 GyE/37 fr/7.5 weeks	NSCLC stage III, unresectable/medically inoperable, KPS 70-100, weight loss not >10% <6months before diagnosis	Stage IIIA, 21; Stage IIIB, 23
Nakayama <i>et al.</i> ³¹ (retrospective, n=35), Japan, Tsukuba	Proton, 155-250MeV, PSc	No	77 GyE/35 fr/7 weeks (n=13), 83.6 GyE/38 fr/7.5 weeks (n=7), 72.6 GyE/22 fr/4.5 weeks (n=6), 74 GyE/37 fr/7.5 weeks (n=3), other (n=6)	NSCLC stage II/III, medically inoperable/ refused surgery, EORTC PS 0-2, unsuitable for/ refusal chemotherapy. Exclusion: pleural effusion, tumour close to stomach/oesophagus	Stage IIA, 2; IIB, 3; Stage IIIA, 12, Stage IIIB, 18
Xiang <i>et al.</i> ³⁴ (prospective, n=84), USA, Houston	Proton, PSc	Concurrent, weekly carboplatin (2AUC) + paclitaxel (50mg/m ²) (n=84). (neo)Adjuvant chemotherapy allowed (n=22)	74 GyE/37/7.5 weeks	Stage III NSCLC, unresectable, availability of pre- and post-treatment PET-CT images.	NR
Oshiro <i>et al.</i> ³⁰ (retrospective, n=57), Japan, Tsukuba	Proton, 200 MeV, PSc	No concurrent chemotherapy, induction chemotherapy: n=14	Median 74 GyE (50-84.5 GyE), median fr dose 2.0 GyE (2.0-6.6 GyE)	Stage III NSCLC	Stage IIIA, 24; Stage IIIB, 33

AUC, area under the curve; EORTC, European Organisation for Research and Treatment of Cancer; fr, fraction(s); KPS, Karnofsky Performance Status; NR, not reported; PS, performance score; PSc, passive scattering; TTD, total tumour dose; USA, United States of America.

In both studies by Iwata *et al*^{24,25}, early stage NSCLC patients were treated with either carbon ions or protons. In their first report, the authors reported the outcome for 80 stage I NSCLC patients treated with 60-80 GyE protons or 52.8 GyE carbon ions during the period 2003-2007²⁴. After restaging based on the AJCC 7th edition of the TNM classification and a longer inclusion and follow-up period (median 51 months), they analysed the outcome for seventy cT2a/2bN0M0 NSCLC patients in a second study²⁵. Some patients in the cohort were therefore included in both studies. The choice of particle type was based on beam availability (during part of the study, only proton beams were available), and if both particle types were available a choice was made after comparison of dose-volume histograms for both modalities.

The American group of Bush *et al*^{14,18,26} has performed three studies on proton beam irradiation for early stage NSCLC in patients with contraindications to surgery or patients refusing surgery. In their first study, they treated 19 patients with insufficient pulmonary reserve or severe cardiac dysfunction with 51 GyE of PBT to the gross tumour volume (GTV). In 18 patients with sufficient cardiopulmonary function, 45 Gy in 1.8 Gy fractions was delivered with photon irradiation, followed by a proton beam boost to the GTV of 28.8 GyE in 1.8 GyE fractions. In 2004 and 2013, updates of the first trial were published, focusing on stage I NSCLC patients treated with proton therapy only^{14,18}. The study published in 2013 investigated the outcome of 111 early stage NSCLC patients, with dose escalation from 51 GyE in 10 fractions to 70 GyE in 10 fractions during the course of the study¹⁸. Nihei *et al* (15) treated 37 stage I patients with PBT in Chiba, Japan. Ten of the included patients were enrolled in an earlier dose escalation study and all patients received 70-94 GyE in 20 fractions (fraction dose 3.5-4.7 GyE).

The use of carbon ions for early stage NSCLC was investigated in four phase II studies by Japanese researchers in a similar study population²⁰⁻²³. Sugane *et al*²³ focused on patients of 80 years or older within the study cohorts of Miyamoto *et al*^{21,22}. The patients received 52.8 GyE (stage IA) or 60 GyE (stage IB) in four fractions during 1 week, or (if treated prior to 2000) 72 GyE in 9 fractions over 3 weeks.

Overall survival and local control

The outcome of the selected studies for early stage NSCLC is summarised in Table 3. The retrospective study by Nakayama *et al*¹⁷ observed 2-year overall survival and local control rates of 97.8% and 97.0%, respectively. However, the study had a relatively short follow-up period (median 17.7 months). No difference in local recurrence between tumours located centrally or peripherally in the lung was observed. Kanemoto *et al*¹⁹ reported a 3 year overall survival of 76.7% and a 3 year local control rate of 81.8% (stage IA 86.2%, stage IB 67%) with a median follow-up period of 31.0 months. The 3 year local control rate was significantly better for peripherally located tumours: 88.4% *versus* 63.9% for centrally located tumours.

Table 3: Study outcomes early stage NSCLC.

Study (characteristics); FU location	OS	LC	DM	PFS	Toxicity
PROTON BEAM ONLY					
Bush <i>et al.</i> ²⁶ (prospective, n=35); USA, Loma Linda	Median 14 months (range 3-45)	2 years 87%	14%*	2 years 63% (Stage I: 86%)	G2 RP: 5.7%
Shiroyama <i>et al.</i> ²⁷ (retrospective, n=51); Japan, Tsukuba	Median 30 months (range 18-153) 2 years Stage I/II: 55%, Stage IA 88%, IB 47% 5 years Stage I/II 23%, IA 70%, IB 16%	5 years 57% (Stage IA 89%, IB 39%)	16%*	5 years 37% (Stage IA 89%, IB 17%)	Acute: lung tox ≤G1: 92%, G2: 6%, G3: 2%
Bush <i>et al.</i> ¹⁴ (phase II, n=68); USA, Loma Linda	At least 12 months 51 GyE: 27%, 60 GyE: 55%	3 years 74% (Stage IA: 87%, IB: 49%)	3 years 31%	3 years 72%	NR
Nihei <i>et al.</i> ¹⁵ (retrospective, n=37); Japan, Chiba	Median 24 months (range 3-62)	1 years 91%, 2 years 80%	19%*	1 year 73%, 2 years 58%	Acute: G1: 84% (mostly dermatitis) No ≥ grade 2 Late: lung toxicity (pneumonitis/pleural effusion): G2: 8% or G3: 8%
Hata <i>et al.</i> ¹⁶ (prospective, n=21); Japan, Tsukuba	Median 25 months (range 10-54)	2 years 74% (Stage IA 100%, IB 90%)	19%*	2 years 79% (Stage IA 89%, IB 70%)	Acute: haematological G1-2: 14%. Dermatitis G1: 19%, RP G2: 5%. Late: G2: 10% (subcutaneous induration/myositis)
Nakayama <i>et al.</i> ¹⁷ (retrospective, n=55) (58 tumours) Japan, Tsukuba	Median 17.7 months (range 1.4-53.3)	2 years 97%	0%	2 years 88.7%, 3 years 78.9%	Acute: lung (pneumonitis) G1: 25.4%, G2: 3.6%, G3: 3.6% Late: rib fracture: 1.8%
Bush <i>et al.</i> ¹⁸ (phase 2, n=111); USA, Loma Linda	Median 48 months 4 years: 51 GyE 18%, 60 GyE 32%, 70 Gy 51%, 4 year OS peripheral T1: 60%	4 years: 60 GyE 45%, 70 Gy 74% Peripheral T1: 96%	4 years peripheral T1: 81%	NR	Rib fractures: 3.6%, no other ≥G2 adverse events
Kanemoto <i>et al.</i> ¹⁹ (retrospective, n=74, 80 tumours), Japan, Tsukuba	Median 31 months (range 7.3-104.3)	3 years 81.8%, 5 years 81.8% 3 years Stage IA 86.2%, IB 67%	NR	3 years 58.6%, 5 years 52.5%	Acute: G2 skin: 2.5%, G2 oesophagitis: 1.3%, G3 RP: 1.3% Late: G3 RP: 1.3%, G3 skin ulcer 1.3%, G4 rib fracture 13.8%

Table 3: Study outcomes early stage NSCLC. (continued)

Study (characteristics); Location	FU	OS	LC	DM	PFS	Toxicity
C-ION (COMBINED WITH PROTON BEAM)						
Iwata <i>et al.</i> ²⁴ (retrospective, n=80), Japan, Hyogo	Median 30.5 months (range 18-66)	3 years 75% (Stage IA 74%, IB 76%). 3 year OS by dose: 80 GyE 90%, 60 GyE 61%, 52.8 GyE 86%	3 years 82% (Stage IA 87%, IB 77%) 3 year LC by dose: 80 GyE 83%, 60 GyE 81%, 52.8 GyE 86%	16 %*	3 years 54% (Stage IA 67%, IB 46%)	Lung toxicity: G2 RP: 11%, G3 RP: 1.3%. Skin: dermatitis G2/3: 16% G2 rib fracture: 23%
Iwata <i>et al.</i> ²⁵ (retrospective, (partially subgroup of cohort Iwata 2010), n=70), Japan, Hyogo	Median 51 months (range 24-103)	4 years 58% (T2a 53%, T2b 67%) Operable patients (n=30): 4 years 72%	4 years 75% (T2a 70%, T2b 84%) Operable patients (n=30): 4 years 73%	20% *	4 years 46% (T2a 43%, T2b 52%) Operable patients (n=30): 4 years 46%	G2/3 RP 3%, G2/3/4 dermatitis 7%, Rib fracture G2 27%, soft tissue fibrosis G2 6%
Miyamoto <i>et al.</i> ²⁰ (phase I/II, n=81, 82 tumours), Japan, Chiba	Median 52.6 months	5 years 42% (Stage IA 64.4%, Stage IB 22%)	23% local recurrence at 6.2- 27.2 months after start RT	38%	NR	Acute: lung G2: 6.2%, G3: 3.7% Late: lung G2: 1.2%
Miyamoto <i>et al.</i> ²¹ (phase II, n=79), Japan, Chiba	Median 38.6 months (range 2.5-72.2)	5 years 45% (Stage IA: 62%, IB 25%)	5 years 90% (Stage IA 98%, IB 80%)	27%*	NR	Acute: lung G2: 1.3% Late: lung G2: 1.3% No G3 toxicity
Miyamoto <i>et al.</i> ²² (phase II, n=50, 51 tumours), Japan, Chiba	Median 59.2 months (range 6-83)	5 years 50% (Stage IA 55.2%, IB 42.9%)	5 years 95%	28%*	NR	Acute: lung toxicity: G1: 2%, G2: 2%, Skin G1: 100% Late: lung G1: 96%, G2: 4%. Skin G1: 98%
Sugane <i>et al.</i> ²³ (phase II, n=28, 29 tumours), Japan, Chiba	NR	2 years 64.3%, 5 years 30.7% (Stage IB 21.2%)	2 and 5 years: 95.8% NR (Stage IA 100%, IB 91.7%). Tumour >4cm: 5 year LC 80%	NR		Acute: no lung toxicity. Skin G1: 96% Late: lung toxicity G1: 96%. Skin G1: 100%

* = own calculation, time-point unknown
DM, distant metastases; FU, follow-up; G, CTC Grade; LC, local control; NR, not reported; OS, overall survival; PFS, progression free survival; RP, radiation pneumonitis; RT, radiotherapy; USA, United States of America.

In their first study in 2010, Iwata *et al*²⁴ reported the outcome for 80 patients treated with either protons or carbon ions with a median follow-up of 30.5 months. They observed 3-year overall survival and local control rates of 75% and 82%, respectively. No significant difference in outcome was observed between the different treatment protocols. The authors also published the long term outcome for cT2a and cT2b NSCLC patients²⁵. They reported a 4-year local control rate of 75%, and overall and progression free survival rates of 58% and 46%, respectively. No significant differences were observed based on T stage. The survival of the operable patients was better than for the medically inoperable patients.

Studies reporting on the use of carbon ions for early stage lung cancer demonstrate 5 year overall survival and local control rates of 45% and 90%, respectively²¹, and of 30.7% and 95.8%²³ for patients aged 80 years or older.

Toxicity

The toxicity of PBT for early stage NSCLC was found to be low, with the percentage of acute and late CTC Grade ≥ 2 adverse events generally $<10\%$. This is not a surprising outcome, since stereotactic body radiation therapy (SBRT) with photons for stage I NSCLC also has a generally favourable toxicity profile¹³. Mainly for peripheral tumours, few treatment related complications have been reported²⁸. The treatment of central tumours located close to vulnerable mediastinal structures, however, can cause a higher rate of severe toxicity²⁹. The LungTech study (NCT01795521) is currently recruiting patients for a phase II trial of hypofractionated photon radiotherapy (60 Gy in 8 fractions given on alternating days) for centrally tumours in patients with inoperable disease. Using PBT, Bush *et al*¹⁸ reported a low incidence of late rib fractures (4%), and in all of the cases the tumour was located close to the chest wall. In contrast, other studies reported a relatively high incidence of Grade ≥ 2 rib fractures of 14-27%^{19,24,25}. In the experience of Iwata *et al*, the rib fractures mainly occurred in patients treated with only one beam portal (24-25). These patients received a rib dose of 70-100% of the isocentre dose.

Locally advanced NSCLC

Study descriptions

Three studies have reported on the outcome of proton therapy for locally advanced NSCLC. The retrospective study of Oshiro *et al*³⁰ evaluated the outcome of patients with stage III NSCLC after treatment with protons, without concurrent chemotherapy. The cohort consisted of 57 patients treated with a median dose of 74 GyE (range 50-85 GyE) in 2 GyE fractions (range 2-6.6 GyE). A respiratory gating system was used and patients were immobilised with a body cast. Due to patient comorbidities, old age or patient refusal, concurrent chemotherapy was not administered. Fourteen patients received

induction chemotherapy, however, without a tumour response. Nakayama *et al*³¹ reported on 35 stage II and III NSCLC patients treated in Tsukuba between 2001 and 2008 with protons to a median dose of 78.3 GyE. All patients were unsuitable for (n=31) or refused chemotherapy or surgery (n=4). Chang *et al*³² performed a phase II study at MD Anderson Cancer Center on the use of protons with concurrent chemotherapy for unresectable Stage III non-small-cell lung cancer. Forty-four stage III NSCLC patients were included and treated with 74 GyE using passively scattered protons, combined with weekly carboplatin and paclitaxel. Treatment simulation with 4-dimensional CT was undertaken and an internal gross tumour volume (iGTV) was defined to account for tumour motion. Verification 4D CT scans were obtained in the third or fourth week of treatment. In case of significant changes regarding patient anatomy or tumour shrinkage, a new treatment plan was constructed (see³³ below).

Overall Survival and local control

After a median follow-up of 22.2 months (for surviving patients) Oshiro *et al*³⁰ reported 1- and 2-year overall survival rates of 65.5% and 39.4%, respectively (Table 4). Progression free survival and local control rates were 24.9% and 64.1% at two years, respectively. Distant metastases were most often the initial sites of recurrence. Induction chemotherapy did not have a significant effect on the overall survival.

For the NSCLC patients included in the study by Nakayama *et al*³¹, the 2-year overall survival was 58.9% and the local progression free survival at 2 years was 65.9%. Four patients (11.4%) developed a recurrence within the irradiated primary tumour volume, ten patients (35%) developed a regional recurrence, and seven patients (20%) developed distant metastases. Chang *et al*³² added concurrent chemotherapy to PBT and reported overall and progression free survival of 86% and 63%, respectively, at one year, and a median overall survival time of 29.4 months. Again, distant metastases were the most frequent site of failure (19 patients, 43%). Only four patients (9.1%) had an isolated local recurrence. OS and PFS were better than those reported by Oshiro *et al*³⁰, possibly due to the added effects of the concurrent chemotherapy or the pre-treatment condition of the patients. While the patients included by Chang *et al*³² were fit enough to receive (concurrent) chemotherapy, most of those described by Oshiro *et al*³⁰ were not (mostly due to old age and comorbidities). In an updated analysis of an expanded cohort of 84 patients treated at MD Anderson Cancer Center with concurrent chemotherapy and PBT for locally advanced NSCLC that assessed the correlation between post-treatment FDG uptake on PET/CT scan and clinical outcomes, including survival, Xiang *et al*³⁴ reported a similar median survival time of 29.9 months. At 3 years, the local recurrence-free survival (LRFS) rate was 34.8%, distant metastasis-free survival (DMFS) rate was 35.4%, progression-free survival (PFS) rate was 31.2%, and the overall survival (OS) rate was

37.2%. Furthermore, post-treatment SUV was found on multivariate analysis to be independently prognostic for LRFS, DMFS, PFS, and OS (all $p < 0.05$).

Table 4: Study outcomes advanced stage NSCLC.

Study (characteristics); location	FU	OS	LC	DM	PFS	Toxicity
PROTON BEAM ONLY						
Bush <i>et al.</i> ²⁶ (prospective, n=35); USA, Loma Linda	Median 14 months (range 3-45)	2 years 31% (IIIA 13%)	2 years 87%	14% *	2 years 63% (IIIA 19%)	G2 RP: 5.7%
Shioyama <i>et al.</i> ²⁷ (retrospective, n=51); Japan, Tsukuba	Median 30 months (range 18-153)	2 years 62%, 5 years 29% 2 years Stage III/IV 62%, 5 years Stage III/IV 0%	5 years 57% (total group)	16%*	5 years 37% (total group)	Acute: lung tox $\leq$ G1: 92%, G2: 6%, G3: 2%
Chang <i>et al.</i> ³² (phase II, n=44), USA, Houston	Median 19.7 months (range 6.1-44.4)	1 year 86%	Local recurrence rate 20.5%	43%	1 year 63%	Acute: CT related G4 tox: 11.4%. G3 dermatitis: 11.4%, G3 oesophagitis: 11.4%, G3 RP: 2.3%. No G4 toxicity. Late: pulmonary/pleural fistula: 2.3%.
Nakayama <i>et al.</i> ³¹ (retrospective, n=35), Japan, Tsukuba	NR	1 year 81.8%, 2 years 58.9%	1 year 93.3%, 2 years 65.9%	20%	1 year 59.6%, 2 years 29.2%	Lung: G1: 25.7%, G2: 14.3%. G2 oesophagitis: 2.9%. No $\geq$ G3 toxicity
Xiang <i>et al.</i> ³⁴ (prospective, n=84), USA, Houston	Median 19.2 months (6.1-52.4)	3 years 37.2%	2 years 83%	39% 3 year DMFS 35.4%	3 years 31.2%	NR
Oshiro <i>et al.</i> ³⁰ (retrospective, n=57), Japan, Tsukuba	Median 16.2 months	1 year 65.5%, 2 years 39.4%	1 year 79.1%, 2 years 64.1%	47%*	1 year 36.2%, 2 years 24.9%	Acute: lung (RP) G2: 7%, G3: 1.8%, G4: 1.8%, G5: 1.8%. Oesophagitis G2: 1.8%. Late: RP G2: 6.3%. Haemoptysis G5: 2.1%

* Own calculation, time-point unknown.

DM, distant metastases; DMFS, distant metastasis free survival; FU, follow-up; G, CTC Grade; LC, local control; NR, not reported; OS, overall survival; PFS, progression free survival; RP, radiation pneumonitis; RT, radiotherapy; USA, United States of America.

Toxicity

Acute treatment toxicity was generally mild. Oshiro *et al*³⁰ reported Grade ≥ 3 lung toxicity in three patients (5%): one patient had Grade 3 pneumonitis effectively treated with steroids, one patient had to discontinue treatment due to Grade 4 pneumonitis and one patient died of pneumonitis during treatment (Grade 5). Both patients with the severe pneumonitis had severe pre-existing interstitial pneumonitis prior to the diagnosis of NSCLC and, therefore, were deemed unsuitable for surgery or conventional (photon) radiotherapy. Three patients developed Grade ≥ 3 late toxicity: two patients with Grade 3 dyspnoea and one patient with Grade 5 haemoptysis (after repeated biopsy of the irradiated bronchus).

In the study by Chang *et al*³², toxicity was primarily related to the administered chemotherapy and consisted mainly of Grade 2 and 3 bone marrow suppression. A further five patients (11.4%) experienced Grade 3 oesophagitis, one patient (2.3%) developed Grade 3 pneumonitis and five patients (11.4%) had Grade 3 dermatitis. One patient developed a pulmonary/pleural fistula. No Grade 5 toxicity occurred. Toxicity was not reported in the expanded analysis by Xiang *et al*. Nakayama *et al*³¹ reported no Grade ≥ 3 toxicities.

PROTON THERAPY TECHNIQUES AND CONSIDERATIONS FOR TREATMENT PLANNING AND DELIVERY

Protons can be delivered with two different radiation techniques: passive scattering proton therapy (PSPT) or pencil beam scanning (PBS). In PSPT the tumour volume is irradiated as a whole, using collimators and compensators for dose conformality. With PBS the target volume is scanned spot-by-spot with a narrow proton beam, enabling intensity modulated proton therapy (IMPT). Most institutions treating NSCLC with protons use the passive technique as it is the most widely available and moreover less sensitive to breathing motion than PBS.

Matney *et al*³⁵ quantified and compared the effects of respiratory motion on clinically delivered IMRT and re-calculated PSPT plans for 20 stage II-IIIb NSCLC patients. For a respiratory motion of up to 17 mm, target coverage was maintained for both IMRT and PSPT. Only two of the studied comparative parameters, lung V5 and spinal cord D_{max} , were statistically significantly better when using PSPT. The authors concluded that PSPT may not be more susceptible to respiratory motion than IMRT.

PSPT also leads to a non-conformal dose-distribution at the proximal edge of the field. Conformality is better for the PBS technique, but the interplay between the intra-

fractional tumour motion and the scanned proton beams can have detrimental effects on the dose distribution. This so-called ‘interplay effect’ can result in severe under- or overdosage: a spot can be irradiated several times or not at all. Thus, the dose is not only inhomogeneous at the edges but also inside the target, and therefore cannot be accounted for by simply adding a surrounding margin³⁶. This is crucial especially for full IMPT that, in contrast to the single field uniform dose (SFUD) technique, results in completely inhomogeneous dose distributions per field. To our knowledge, only the MD Anderson Cancer Center has started to treat NSCLC with PBS using the SFUD technique, limiting the treatment to a subset of tumours with motion amplitudes below 5 mm. Li *et al*³⁷ investigated the extent of the interplay effect on IMPT delivery and concluded that for the specific system at MDACC, this effect may not be a primary concern. Grassberger *et al*³⁸ and Dowdell *et al*³⁹ have reported that the magnitude of the interplay effect depends on patient parameters such as motion amplitude and beam delivery parameters such as spot size. Several techniques (rescanning, gating, tracking) trying to compensate for the interplay effect are topic of intensive research in several groups worldwide. For IMPT, the robustness and a geometrical tumour tracking method mitigating to motion were evaluated in 7 NSCLC patients treated to 45 GyE in 3 fractions⁴⁰. Patients had in total nine peripheral stage I lung tumours that were imaged with 4D-CT, and the combined dose distribution was summed using deformable image registration. Additionally, plans were constructed in which the proton beams were geometrically shifted without adjusting the beam energy. In 6 tumours showing a displacement of < 1 cm, 97-100% of the GTV was covered by 95% of the prescribed dose. For the remaining 3 patients, this was 95%, 82% and 51%, respectively; subsequently, the application of a geometrical tracking method improved this to 100%, 98% and 97%, respectively. The authors concluded that the simple tracking method was valuable for improving GTV coverage. The practicalities and limitations of tracking and gating techniques in IMPT have also been reported by the group at Paul Scherrer Institute^{41,42}.

Another key aspect is plan robustness, meaning the susceptibility of the nominal treatment plan due to uncertainties (*e.g.*, setup uncertainties) or motion. Some treatment planning systems already allow the evaluation of plan robustness. Furthermore, consideration of robustness cannot only be included in the treatment plan evaluation step, but also in the plan optimisation (robust optimisation)⁴³⁻⁴⁶. Usually this will result in decreased quality of the nominal treatment plan in combination with smaller deviations between nominal and actual dose distribution under the influence of setup uncertainties and intra- and inter-fractional motion.

For PSPT, range and set-up uncertainties can be taken into account by widening the aperture to ensure the lateral coverage in the presence of set-up and /or in-patient

target shifts. Furthermore, density changes lateral to the beam path, *e.g.*, due to intra-fractional motion, are mitigated by “smearing” the compensator. Range uncertainties are accounted for by increasing the nominal range. This method was investigated by several groups^{9,47} and is widely accepted in PSPT in the clinic^{8,48-50}.

For PBS no physical devices are used. Consequently, a different method needs to be applied to compensate for range and set-up uncertainties. Laterally, an increased treatment area adding a margin to the tumour volume is applicable. For range uncertainties a more sophisticated approach is the use of field-specific PTVs that take into account the influences of range uncertainty for each treatment field separately^{10,51,52}. In comparison to a uniform margin extension this leads to a PTV that can compensate for the specific requirements in proton therapy and thus preserve the target coverage in the presence of uncertainties.

(IN SILICO) COMPARATIVE STUDIES

Various institutions employing particle therapy or in the process of setting up the facility have published findings on comparative *in silico* planning studies using different photon and proton delivery techniques. Kase *et al*⁵³ compared PSPT with IMPT in a variety of primary tumour sites, including NSCLC. IMPT resulted in lower dose to organs at risk, specifically, the high dose to the skin, the D20 to the normal lung, and the spinal cord.

Early stage NSCLC

Wang and colleagues⁵⁴ from the Proton Medical Research Center compared 3D-CRT to PSPT in 24 patients with peripheral stage I NSCLC. Two to four proton beam ports were used and irradiation was applied at end exhalation. Photons were delivered using 5 to 7 coplanar ports covering the same clinical and planning target volume (CTV and PTV, respectively). The prescribed dose was 66 GyE in 10 fractions at the isocentre. While the 90% isodose line covered >99% of the CTV for both treatment modalities, the 95% isodose line covered only 86.4% of the CTV for proton plans and 43.2% for 3D-CRT plans. Organ at risk (OAR) doses, specifically, lungs, heart, oesophagus, and spinal cord, were significantly lower for the proton beam technique.

The Mayo Clinic Group⁵⁵ generated treatment plans for eight stage I NSCLC patients with peripheral lung nodules using photon SBRT, and one-, two-, and three-field passively scattered or actively scanned proton beams. For SBRT (3 x 20 Gy), 10 or more noncoplanar beams were manually selected to achieve optimal PTV coverage while minimising dose to the OARs. Plans were normalised to isocentre with the prescription isodose

line covering 95% or more of the PTV. For proton beam treatment, beam direction was manually optimised to maximise access to the tumour while minimising exposure to OARs and adjacent normal tissues. Proton beam plans demonstrated significantly lower maximum and higher minimum PTV doses compared with SBRT. With the exception of the three-field actively scanned approach, the maximum dose 2 cm from the PTV was significantly higher with protons beams. The doses to OARs (lungs, spinal cord, heart, bronchial tree, oesophagus, skin, and ribs) were generally lower with protons than with photons. Using actively scanned beams, the maximum dose to the PTV, V30 Gy, and the dose to any tissue 2 cm from the PTV decreased, while the minimum dose to the PTV increased.

Similarly, Kadoya *et al*⁵⁶ studied 21 patients with peripheral stage I NSCLC, delivering a dose of 66 GyE in 10 fractions during maximal expiration using SBRT (7-8 noncoplanar 4-MV photon beams) or PSPT (2-3 directions). While the dose to the PTV was non-significantly different, the dose to the lung was significantly lower with the PSPT technique. The authors concluded that PSPT may be advantageous for large or multiple PTVs.

For stage I NSCLC, proton beam therapy may provide the greatest dosimetric and clinical benefit for patients with centrally-located tumours given the higher reported toxicity when delivering SBRT for tumours in this region. For centrally and superiorly located stage I NSCLC, Register *et al*.⁵⁷ compared SBRT with PSPT and IMPT. SBRT was prescribed to 50 Gy in 12.5-Gy fractions, normalised such that 95% of the PTV received 100% of the prescribed dose. Each PSPT plan was created with three to four coplanar beam angles in an attempt to minimise the exit dose into the lung parenchyma. The same beam angles were used for generating the IMPT plans. Only 6 of 15 photon SBRT plans satisfied PTV coverage and all normal tissue dose constraints, compared to 12 PSPT and 14 IMPT plans.

A significant reduction in the normal tissue dose by passively scattered protons (66 GyE) compared to 3D-CRT or IMRT photon treatment (66 Gy) was reported by Chang *et al*⁵⁸ for stage I and stage IIIA/B NSCLC patients. For early stage NSCLC (n=10), the DVH comparison revealed a reduction in dose to the ipsilateral and contralateral lungs, heart, spinal cord and oesophagus with protons. For locally advanced patients (n=15) in all cases, the doses to lung, heart, oesophagus, spinal cord, and integral dose were lower with proton therapy than both 3D-CRT and IMRT photon modalities. This dosimetric benefits of protons over photons persisted even when escalating the PBT doses to 87.5 GyE for stage I NSCLC and 74 GyE for stage III NSCLC compared with 66 Gy for all photon plans.

An *in silico* planning study comparing modern photon techniques with protons and carbon ions in 25 stage I NSCLC patients is currently being conducted by the ROCOCO consortium (NCT02038413).

Locally advanced NSCLC

Proton beam therapy may be advantageous for locally advanced NSCLC patients delivering either the same dose with less toxicity or a higher dose under isotoxic conditions. Representative images showing plan comparisons for patients with locally advanced non-small cell lung cancer, are shown in Figures 1 and 2. In the first, PSPT spares significant volumes of heart, oesophagus and lung relative to IMRT. In the latter comparing IMRT, PSPT and PBS using SFUD the dose to the heart, spinal cord and contralateral lung is significantly reduced using (advanced) proton techniques.

The MD Anderson Cancer Center conducted a prospective phase II clinical study combining chemotherapy with PSPT in 44 unresectable NSCLC patients (details and outcome of the study described earlier³²). Koay *et al*³³ published an analysis for the nine out of 44 patients for whom the plans were adapted during the treatment course. While the authors observed profound differences in the dose to the oesophagus and spinal cord, no statistical comparison of the adapted versus non-adapted patients was performed. For two of the nine patients, the internal CTV coverage would have decreased significantly without adaptation. Remarkably, the reported toxicity was higher among the patients treated with adaptive plans, although statistical comparison was again lacking. Treatment outcome was not significantly different between the treatment strategies ($P < 0.05$).

Zhang *et al*⁵⁹ compared IMPT with PSPT and IMRT in 20 NSCLC patients with extensive stage IIIB disease. Using IMRT, the selected patients had no or borderline tolerance to IMRT at 60-63 Gy when keeping within the normal tissue dose constraints. IMPT succeeded in sparing more lung, heart, spinal cord, and oesophagus when maintaining the prescribed dose. IMPT was even feasible when escalating the dose up to 83.5 Gy (mean maximum tolerated dose 74 Gy) whereas PSPT was limited by the oesophagus dose constraint (74 Gy). The University of Florida Proton Therapy Institute⁶⁰ compared 3D-CRT with IMRT and PSPT in 8 NSCLC patients. The target dose prescription was achieved in all patients using either of the techniques. Compared to the photon techniques, PSPT considerably reduced the dose to radiation-sensitive normal structures: normal lung V20 Gy by median 29% for 3D-CRT and 26% for IMRT, mean lung dose by 33% and 31%, and V10 Gy bone marrow by 30% and 27%, respectively. This may offer an advantage in patients undergoing sequential or concurrent radiochemotherapy. In a multicentric *in silico* clinical trial, the ROCOCO consortium compared photon (3D-CRT and IMRT) with proton (PSPT) treatment for stage IA-IIIB NSCLC patients delivering 70 Gy in 35 fractions⁸.

Figure 1: Treatment planning images and dose-volume histogram comparison (Hospital of the University of Pennsylvania). Representative treatment planning images for a patient with locally advanced non-small cell lung cancer with a right lower lobe primary tumour (iGTV primary tumour depicted as a yellow contour) and multi-station mediastinal nodal metastasis (iGTV nodal metastasis depicted as a pink contour). The composite PTV is depicted as a cyan contour. Comparative plans for IMRT (left) and proton beam therapy (right) are depicted in the axial planes (top row), sagittal planes (middle row), and coronal planes (bottom row) delivering 66.6 Gy (IMRT) or 66.6 GyE (proton therapy) in 37 fractions. Dose colour wash coding: blue = 50% to red = global max above 100%. Representative dose-volume histograms for the same patient are also depicted showing dose to target volumes of PTV (green) and ITV (cyan) and dose to normal structures of heart (orange), total lung minus GTV (purple), oesophagus (light blue), and spinal cord (dark blue) for IMRT (triangle) and proton (square) plans.

Figure 2: Treatment plan comparison between IMRT (left upper row), PSPT (right upper row) and PBS using SFUD (left lower row) in an advanced-stage NSCLC patient (OncoRay, Dresden). The planning target volume (PTV) is represented by the white contour. Furthermore a Dose-Volume-Histogram (DVH; right lower row) analysis is illustrated for the three treatment techniques showing the clinical target volume (CTV; red), PTV (dark red), ipsilateral lung (blue), spinal cord (orange), heart (pink), contralateral lung (turquoise).

The integral dose for the photon techniques was higher than for the proton techniques, whereas the mean lung dose was lower for protons. For 10 patients, dose escalation to the primary tumour up to 87 Gy was feasible for all three modalities; however, the mean lung and integral doses were higher for photons than for protons.

CONCLUSION

Proton beam delivery has evolved rapidly over the last decade, enabling highly conformal treatment delivery with the possibility of escalating the dose to the primary tumour while maintaining the dose to the normal tissues, or maintaining the dose to the target volume and reducing the dose to the organs at risk. Dosimetric advantages of protons over photons have been demonstrated across NSCLC stages of disease in reducing doses to critical organs at risk, including the lungs, heart, oesophagus, and spinal cord. Proton

beam therapy has also been used clinically in an increasing number of prospective studies for both stage I NSCLC and locally advanced NSCLC with a generally more favourable toxicity profile than what has been reported with historical photon studies. Particle beam treatment may prove to provide its greatest clinical benefit compared with IMRT and photon treatment techniques for patients with pre-treatment severe functional impairments (*e.g.*, poor lung function, pre-existing lung disease), when delivering escalating doses of radiation therapy or using radiation therapy as part of trimodality therapy combined with chemotherapy and surgery, and for definitive re-treatment of NSCLC patients with a local/locoregional recurrence following prior radiotherapy. From the *in silico* trials we have gathered, we can conclude that the dose distributions with IMPT are superior to those of the photon treatments and the passive scattering technique. Until now, PSPT has predominantly been used in the clinic instead of IMPT. It is likely that a more widespread introduction of IMPT can provide further improvement in lung cancer outcome and/or decreased toxicity, through increased precision and personalised treatment, provided that range uncertainties are well accounted for.

REFERENCES

1. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA: a cancer journal for clinicians*. 2014.
2. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(13):2181-2190.
3. Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2012;7(4):716-722.
4. Kong FM, Zhao J, Wang J, Faivre-Finn C. Radiation dose effect in locally advanced non-small cell lung cancer. *Journal of thoracic disease*. 2014;6(4):336-347.
5. van Baardwijk A, Wanders S, Boersma L, 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(8):1380-1386.
6. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011;100(1):76-85.
7. Hoffmann AL, Troost EG, Huizenga H, Kaanders JH, Bussink J. Individualized dose prescription for hypofractionation in advanced non-small-cell lung cancer radiotherapy: an in silico trial. *International journal of radiation oncology, biology, physics*. 2012;83(5):1596-1602.
8. Roelofs E, Engelsman M, Rasch C, et al. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2012;7(1):165-176.
9. Moyers MF, Miller DW, Bush DA, Slater JD. Methodologies and tools for proton beam design for lung tumors. *International journal of radiation oncology, biology, physics*. 2001;49(5):1429-1438.
10. Park PC, Zhu XR, Lee AK, et al. A beam-specific planning target volume (PTV) design for proton therapy to account for setup and range uncertainties. *International journal of radiation oncology, biology, physics*. 2012;82(2):e329-336.
11. van Baardwijk A, Tome WA, van Elmpt W, et al. Is high-dose stereotactic body radiotherapy (SBRT) for stage I non-small cell lung cancer (NSCLC) overkill? A systematic review. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;105(2):145-149.
12. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman B, Senan S. Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2011;101(2):240-244.
13. Palma D, Senan S. Stereotactic radiation therapy: changing treatment paradigms for stage I nonsmall cell lung cancer. *Current opinion in oncology*. 2011;23(2):133-139.
14. Bush DA, Slater JD, Shin BB, Cheek G, Miller DW, Slater JM. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest*. 2004;126(4):1198-1203.
15. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2006;65(1):107-111.

16. Hata M, Tokuyue K, Kagei K, et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. *International journal of radiation oncology, biology, physics*. 2007;68(3):786-793.
17. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for patients with medically inoperable stage I non-small-cell lung cancer at the university of tsukuba. *International journal of radiation oncology, biology, physics*. 2010;78(2):467-471.
18. Bush DA, Cheek G, Zaheer S, et al. High-dose hypofractionated proton beam radiation therapy is safe and effective for central and peripheral early-stage non-small cell lung cancer: results of a 12-year experience at Loma Linda University Medical Center. *International journal of radiation oncology, biology, physics*. 2013;86(5):964-968.
19. Kanemoto A, Okumura T, Ishikawa H, et al. Outcomes and prognostic factors for recurrence after high-dose proton beam therapy for centrally and peripherally located stage I non--small-cell lung cancer. *Clinical lung cancer*. 2014;15(2):e7-12.
20. Miyamoto T, Yamamoto N, Nishimura H, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2003;66(2):127-140.
21. Miyamoto T, Baba M, Sugane T, et al. Carbon ion radiotherapy for stage I non-small cell lung cancer using a regimen of four fractions during 1 week. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2007;2(10):916-926.
22. Miyamoto T, Baba M, Yamamoto N, et al. Curative treatment of Stage I non-small-cell lung cancer with carbon ion beams using a hypofractionated regimen. *International journal of radiation oncology, biology, physics*. 2007;67(3):750-758.
23. Sugane T, Baba M, Imai R, et al. Carbon ion radiotherapy for elderly patients 80 years and older with stage I non-small cell lung cancer. *Lung cancer*. 2009;64(1):45-50.
24. Iwata H, Murakami M, Demizu Y, et al. High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer. *Cancer*. 2010;116(10):2476-2485.
25. Iwata H, Demizu Y, Fujii O, et al. Long-term outcome of proton therapy and carbon-ion therapy for large (T2a-T2bN0M0) non-small-cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2013;8(6):726-735.
26. Bush DA, Slater JD, Bonnet R, et al. Proton-beam radiotherapy for early-stage lung cancer. *Chest*. 1999;116(5):1313-1319.
27. Shioyama Y, Tokuyue K, Okumura T, et al. Clinical evaluation of proton radiotherapy for non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2003;56(1):7-13.
28. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA : the journal of the American Medical Association*. 2010;303(11):1070-1076.
29. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(30):4833-4839.
30. Oshiro Y, Mizumoto M, Okumura T, et al. Results of proton beam therapy without concurrent chemotherapy for patients with unresectable stage III non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2012;7(2):370-375.
31. Nakayama H, Satoh H, Sugahara S, et al. Proton beam therapy of Stage II and III non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2011;81(4):979-984.

32. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer*. 2011;117(20):4707-4713.
33. Koay EJ, Lege D, Mohan R, Komaki R, Cox JD, Chang JY. Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. *International journal of radiation oncology, biology, physics*. 2012;84(5):1093-1100.
34. Xiang ZL, Erasmus J, Komaki R, Cox JD, Chang JY. FDG uptake correlates with recurrence and survival after treatment of unresectable stage III non-small cell lung cancer with high-dose proton therapy and chemotherapy. *Radiation oncology*. 2012;7:144.
35. Matney J, Park PC, Bluett J, et al. Effects of respiratory motion on passively scattered proton therapy versus intensity modulated photon therapy for stage III lung cancer: are proton plans more sensitive to breathing motion? *International journal of radiation oncology, biology, physics*. 2013;87(3):576-582.
36. Bert C, Grozinger SO, Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Physics in medicine and biology*. 2008;53(9):2253-2265.
37. Li Y, Kardar L, Li X, et al. On the interplay effects with proton scanning beams in stage III lung cancer. *Medical physics*. 2014;41(2):021721.
38. Grassberger C, Dowdell S, Lomax A, et al. Motion interplay as a function of patient parameters and spot size in spot scanning proton therapy for lung cancer. *International journal of radiation oncology, biology, physics*. 2013;86(2):380-386.
39. Dowdell S, Grassberger C, Sharp GC, Paganetti H. Interplay effects in proton scanning for lung: a 4D Monte Carlo study assessing the impact of tumor and beam delivery parameters. *Physics in medicine and biology*. 2013;58(12):4137-4156.
40. Munck af Rosenschold P, Aznar MC, Nygaard DE, et al. A treatment planning study of the potential of geometrical tracking for intensity modulated proton therapy of lung cancer. *Acta oncologica*. 2010;49(7):1141-1148.
41. van de Water S, Kreuger R, Zenklusen S, Hug E, Lomax AJ. Tumour tracking with scanned proton beams: assessing the accuracy and practicalities. *Physics in medicine and biology*. 2009;54(21):6549-6563.
42. Schatti A, Zakova M, Meer D, Lomax AJ. The effectiveness of combined gating and re-scanning for treating mobile targets with proton spot scanning. An experimental and simulation-based investigation. *Physics in medicine and biology*. 2014;59(14):3813-3828.
43. Liu W, Frank SJ, Li X, et al. Effectiveness of robust optimization in intensity-modulated proton therapy planning for head and neck cancers. *Medical physics*. 2013;40(5):051711.
44. Engelsman M, Schwarz M, Dong L. Physics controversies in proton therapy. *Seminars in radiation oncology*. 2013;23(2):88-96.
45. Stuschke M, Kaiser A, Pottgen C, Lubcke W, Farr J. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2012;104(1):45-51.
46. Unkelbach J, Bortfeld T, Martin BC, Soukup M. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. *Medical physics*. 2009;36(1):149-163.
47. Engelsman M, Rietzel E, Kooy HM. Four-dimensional proton treatment planning for lung tumors. *International journal of radiation oncology, biology, physics*. 2006;64(5):1589-1595.
48. Hoppe BS, Flampouri S, Henderson RH, et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clinical lung cancer*. 2012;13(5):352-358.

49. Seco J, Panahandeh HR, Westover K, Adams J, Willers H. Treatment of non-small cell lung cancer patients with proton beam-based stereotactic body radiotherapy: dosimetric comparison with photon plans highlights importance of range uncertainty. *International journal of radiation oncology, biology, physics*. 2012;83(1):354-361.
50. Hui Z, Zhang X, Starkschall G, et al. Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer. *International journal of radiation oncology, biology, physics*. 2008;72(5):1385-1395.
51. Knopf AC, Boye D, Lomax A, Mori S. Adequate margin definition for scanned particle therapy in the incidence of intrafractional motion. *Physics in medicine and biology*. 2013;58(17):6079-6094.
52. Bert C, Rietzel E. 4D treatment planning for scanned ion beams. *Radiation oncology*. 2007;2:24.
53. Kase Y, Yamashita H, Fuji H, et al. A treatment planning comparison of passive-scattering and intensity-modulated proton therapy for typical tumor sites. *Journal of radiation research*. 2012;53(2):272-280.
54. Wang C, Nakayama H, Sugahara S, Sakae T, Tokuyue K. Comparisons of dose-volume histograms for proton-beam versus 3-D conformal x-ray therapy in patients with stage I non-small cell lung cancer. *Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft [et al]*. 2009;185(4):231-234.
55. Macdonald OK, Kruse JJ, Miller JM, et al. Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *International journal of radiation oncology, biology, physics*. 2009;75(3):950-958.
56. Kadoya N, Obata Y, Kato T, et al. Dose-volume comparison of proton radiotherapy and stereotactic body radiotherapy for non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2011;79(4):1225-1231.
57. Register SP, Zhang X, Mohan R, Chang JY. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2011;80(4):1015-1022.
58. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2006;65(4):1087-1096.
59. Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. *International journal of radiation oncology, biology, physics*. 2010;77(2):357-366.
60. Nichols RC, Huh SN, Henderson RH, et al. Proton radiation therapy offers reduced normal lung and bone marrow exposure for patients receiving dose-escalated radiation therapy for unresectable stage III non-small-cell lung cancer: a dosimetric study. *Clinical lung cancer*. 2011;12(4):252-257.

CHAPTER 6

Photons, protons or carbon ions for stage I non-small cell lung cancer? Results of the multicentric ROCOCO *in silico* study

Krista C.J. Wink, Erik Roelofs, Charles B. Simone II, David Dechambre, Alina Santiago, Judith van der Stoep, Wim Dries, Julia Smits, Stephen Avery, Filippo Ammazalorso, Nicolas Jansen, Urszula Jelen, Timothy Solberg, Dirk de Ruyscher, Esther G.C. Troost

Radiotherapy & Oncology 2018; 128: 139-146

ABSTRACT

Purpose

To compare dose to organs at risk (OARs) and dose-escalation possibility for 24 stage I non-small cell lung cancer (NSCLC) patients in a ROCOCO (Radiation Oncology Collaborative Comparison) trial.

Methods

For each patient, 3 photon plans [Intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and CyberKnife], a double scattered proton (DSP) and an intensity-modulated carbon-ion (IMIT) therapy plan were created. Dose prescription was 60Gy (equivalent) in 8 fractions.

Results

The mean dose and dose to 2% of the clinical target volume (CTV) were lower for protons and ions compared with IMRT ($p < 0.01$). Doses to the lungs, heart, and mediastinal structures were lowest with IMIT ($p < 0.01$), doses to the spinal cord were lowest with DSP ($p < 0.01$). VMAT and CyberKnife allowed for reduced doses to most OARs compared with IMRT. Dose escalation was possible for 8 patients. Generally, the mediastinum was the primary dose-limiting organ.

Conclusion

On average, the doses to the OARs were lowest using particles, with more homogenous CTV doses. Given the ability of VMAT and CyberKnife to limit doses to OARs compared with IMRT, the additional benefit of particles may only be clinically relevant in selected patients and thus should be carefully weighed for every individual patient.

INTRODUCTION

The introduction of stereotactic ablative radiation therapy (SABR) has led to an increase in radiotherapy use in early stage non-small cell lung cancer (NSCLC) patients and fewer untreated patients, which has driven up population-based survival for lung cancer¹. SABR is a form of high-precision radiotherapy, using large (ablative) radiation doses per fraction, generally in one to eight fractions over one to three weeks. A Biologically Effective Dose (BED) of more than 100Gy has allowed for high local tumour control rates (>90%), comparable to those obtained with surgery, supporting its consideration in operable patients²⁻⁴. A pooled meta-analysis of the STARS and ROSEL trials has indicated non-inferiority of SABR compared to surgery with respect to survival and disease progression, albeit in a small patient population with limited follow up. Furthermore, treatment related toxicity was generally low and found to be favourable compared to surgery, even though damage to central structures and the chest wall have been reported^{4,5}. The photon-based SABR techniques have evolved over the years from 3-dimensional (3D) conformal photon radiotherapy (3D-CRT) to intensity-modulated radiotherapy (IMRT), and volumetric modulated arc therapy (VMAT).

In recent years, there has been a massive expansion in particle therapy centres (mainly proton therapy) in clinical operation. Charged particles are characterised by the presence of the so-called 'Bragg peak', *i.e.*, dose deposition at an energy-dependent tissue depth, and a sharp dose falloff at the distal edge with no further dose deposition. Some centres use particles for (stereotactic) treatment of lung cancer and report outcomes seemingly comparable to photon radiotherapy despite the known difficulties with the delivery of particle beams to a moving tumour in the lung (e.g. range uncertainties, interplay effect)^{6,7}. Several dosimetric studies on particles have shown a significant reduction in dose to surrounding organs at risk (OAR) and thus short- and long-term toxicities⁸⁻¹².

While there are multiple options for delivery of photon- or particle-based radiation therapy in early stage lung cancer patients, it is currently not known which technique is best in terms of target coverage and low dose to OARs. A randomised controlled trial comparing these techniques would require a very large patient cohort to show significant differences in local control and/or toxicity and likely be fraught with accrual difficulties. Hence, the multicentre international Radiation Oncology Collaborative Comparison (ROCOCO) was initiated in 2007 conducting several comparative *in silico* trials in multiple primary tumour sites, including lung cancer^{8,13}.

In this study on twenty-five patients with stage I NSCLC, we compared the doses to the OARs and the dose escalation probability for one SABR fractionation schedule using five contemporary radiotherapy techniques with either photons (IMRT, VMAT and CyberKnife), double scattered protons (DSP) or intensity-modulated carbon ions (IMIT).

PATIENTS AND METHODS

Patients

Twenty-five consecutive patients with stage I NSCLC who underwent SABR at MAASTRO clinic (Department of Radiotherapy, Maastricht University Medical Center+, The Netherlands) between February 2011 and June 2013 were included in this *in silico* planning study. The maximum tumour diameter was 3 cm and all tumours were at least 2 centimetres separated from the mediastinal structures and bronchial tree¹⁴. Most tumours were located peripherally, with 15 tumours (or their planning target volume; PTV) overlapping chest wall and ribs. This retrospective *in silico* planning study was approved by the Institutional Review Board of MAASTRO clinic.

Target and OAR definitions

Delineation of the target volumes and OARs was performed at MAASTRO clinic according to institutional guidelines. The OARs, gross tumour volume (GTV), clinical target volume (CTV) and PTV were delineated in the mid-ventilation phase of a four-dimensional-18F fluorodeoxyglucose positron emission tomography-computed tomography (4D-FDG-PET-CT) scan. For this purely dosimetric comparison between the modalities, a gated treatment was assumed without the use of an internal target volume (ITV) accounting for breathing motion. The following dose limiting OARs were delineated: the mediastinum (consisting of heart, great vessels, trachea, main bronchi and oesophagus), lungs, oesophagus, spinal cord and brachial plexus. The 'mediastinum' was expanded 5 mm to create a planning risk volume (PRV mediastinal envelope) to account for setup inaccuracy or movement. The ribs were contoured within 5 cm of the PTV (excluding the intercostal space;¹⁵). The chest wall constituted of a 1.5-centimeter expansion from the lungs. For comparison of the total lung dose, the GTV was subtracted from the total lung volume.

Treatment planning

For each patient, three photon plans (IMRT, VMAT and Cyberknife), a DSP plan and an IMIT plan were calculated at Catherina Hospital Eindhoven (CHE; the Netherlands), MAASTRO clinic, the Centre Hospitalier Universitaire de Liège (CHU; Belgium), the Hospital of the University of Pennsylvania (UPENN; USA), and the University Hospital of Marburg (UHM; Germany), respectively.

Irrespective of the clinically used dose, the prescribed dose was 60 Gy in 8 fractions, achieving a Biologically Effective Dose (BED) of 105 Gy, roughly equivalent to 87.5 Gy in 2 Gy fractions (EQD₂). Each centre used their in house, clinically commissioned treatment planning system (TPS) assuring state-of-the-art dose calculations. Planning

objectives were in accordance with several multi-institutional trials (e.g. RTOG 0618 and RTOG 0236), where 95% of the PTV should receive at least 100% of the prescribed dose, and the maximum dose ($D_{\max}$) was not to exceed 140%. The dose was prescribed to the given PTV by all centres except for UPENN, which employed individualised uncertainty margins for DSP. According to the study protocol, the dose to the CTV was eventually evaluated. In order to guarantee uniform CTV dose level enabling comparison of the dose to the surrounding OARs, all plans were rescaled such that 99% of the CTV received 60 Gy (RBE equivalent).

For the OARs, consensus constraints were defined *a priori* among investigators from all centres prior to planning and largely mirrored 8-fraction radiotherapy institutional constraints: spinal cord, ≤ 32 Gy to 0.03 cm^3 ; oesophagus and PRV mediastinal envelope, ≤ 41 Gy to 0.03 cm^3 ; heart, ≤ 46 Gy to 0.03 cm^3 ; volume of 'healthy' lungs (total lungs minus GTV) $V_{20\text{Gy}} < 15\%$; brachial plexus, ≤ 38 Gy to 0.03 cm^3 (delineated only for case where the caudal border of the brachial plexus was within 5 cm of the PTV); and cardiac device (if present) $D_{\max} = 2$ Gy. Planning objectives for the thoracic wall included: ribs: $V_{32.5\text{Gy}} < 1 \text{ cm}^3$ and $D_{\max} = 35$ Gy; chest wall: $V_{32.5\text{Gy}} < 30 \text{ cm}^3$ and $D_{\max} = 40$ Gy. The following priorities were set for the objectives (numbered in order of decreasing importance): 1 = spinal cord, 2 = brachial plexus, 3 = lungs, 4 = PRV mediastinal envelope, 5 = ribs, 6 = chest wall, 7 = oesophagus, and 8 = heart.

Photons

The step-and-shoot IMRT plans were calculated using Pinnacle v. 9.6 (Philips Radiation Oncology Systems, Fitchburg, WI). Five to seven (mainly equispaced) 6MV photon beams were employed, avoiding beam entrance through the contralateral lung. The VMAT plans were created using Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The plans generally consisted of two 180 degree arcs with an energy of 10MV. CyberKnife plans were created using Multiplan v. 5.2.1 (Accuray Inc., Sunnyvale, CA). The non-coplanar beam arrangement was chosen from a large set of predefined nodes (full-path). A maximum of three collimators were used and the collimator diameter was case dependent (usually ranging from 60 to 80% of the largest PTV diameter).

Protons

In the DSP plans, the relative biological effectiveness (RBE) doses were calculated using an RBE of 1.1 for protons using Eclipse v. 11.0 (Varian Medical Systems). The field size was limited to 12 cm. Beam arrangements were chosen based on the path of least variation. PTV margins were determined by range * 3.5% plus 3mm. Portals were designed to avoid OARs distal to the target. Plans used 2-3 fields as a trade-off between treatment time and target conformity.

Carbon ions

The IMIT plans were calculated at the UHM using Syngo PT Planning (Siemens Health Care Systems, Erlangen, Germany), typically using 3 or 4 fields with a patient-specific beam arrangement assuming the use of a gantry. The RBE was calculated using the first version of the Local Effect Model (LEM1). The following spot scanning parameters were employed: a nominal spot size of 8mm, a scanning grid and energy step size of 3mm. The base data (e.g. energy range) used for planning was representative of facilities such as the ion-beam therapy centres in Heidelberg and Marburg.

Data storage and analysis

The Multicentric *In Silico* Trials In Radiotherapy (MISTIR) framework (<http://www.mistir.info>) was used for data storage and exchange. The datasets were downloaded from the MISTIR database by the participating ROCOCO partners to perform treatment planning. After completion of the treatment plans, the dose matrices were re-uploaded to the database in DICOM format (Digital Imaging and Communication in Medicine). The dose-volume metrics were extracted and compared to the IMRT plans, which was considered as the 'gold standard'. The following parameters were compared for CTVs: mean dose (D_{mean}); highest dose to 2% of the volume ($D_{2\%}$, near maximum dose), lowest dose to 98% of the volume ($D_{98\%}$, near minimum dose); and OARs: minimum dose to the 'hottest' 0.03 cm³ ($D_{0.03\text{cc}}$, near maximum dose), $V_{5\text{Gy}}$ and $V_{20\text{Gy}}$. To quantitatively assess the differences in conformity between the five modalities, conformation numbers (CN) were calculated for the CTV. The CN calculations were based on the formula described by van 't Riet *et al.*^{8,16}, rewritten as follows: $\text{CN}_{x\%} = (\text{CTV}_{x\%}/\text{CTV}) * (\text{CTV}_{x\%}/V_{x\%})$, where $\text{CTV}_{x\%}$ and $V_{x\%}$ represent the volume of the CTV or the overall volume, respectively, receiving a percentage (x%) of the prescribed dose. The CNs were calculated for $x = 50\%$, 80% and 95% .

The dose escalation probability was assessed for each patient by upscaling the plans until reaching the constraint of any of the OARs, thereby reaching the maximum tolerated dose (MTD). Dose escalation was performed only if there was room for escalation for all modalities. The volume dependent constraints (e.g., $V_{20\text{Gy}}$) were not incorporated in the MTD calculations, because rescaling would not suffice for these dose-volume-histogram dependent values, but instead, re-planning would be required, which was beyond the scope of this *in silico* planning study. To test for statistical significance, a two-sided Wilcoxon signed rank test was used with a Bonferroni-corrected p-value <0.01 to adjust for multiple comparisons. Data evaluation and statistical analysis were performed using Matlab software (v. 2016b, the Math Works, Natick, MA).

RESULTS

Due to a technical obstacle, only twenty-four out of the 25 datasets were available for analysis. The mean CTV was 20.7 cm³ (range 5.34-71.01 cm³). The anatomical distribution of the 24 lung tumours is shown in Figure 1A-C. The mean dose to the target volumes and OARs after rescaling the dose to 99% of the CTV receiving at least 60 Gy are shown in Table 1. Mid-CTV dose distributions for a typical case are shown in Figure 2. The D_{mean} and $D_{2\%}$ to the CTV were significantly lower for DSP and IMIT than for IMRT, reflecting a better dose homogeneity with particles ($p=0.002$ and $p=0.004$, respectively, for DSP; $p<0.001$ and $p<0.001$, respectively, for IMIT; Table 1). D_{mean} and $D_{2\%}$ were higher in the Cyberknife plans compared to IMRT (both $p<0.001$). The CNs revealed worse conformality for the DSP plans, for the tested 50%, 80% and 90% isodose levels (Table 1).

Figure 1A-C: Anatomical tumour distribution of all 24 patients, A) right lung, lateral view (14 tumours); B) anterior view, C) left lung, lateral view (10 tumours). In both lateral views, the bold and italic numbers represent lateral tumours. In the anterior view, the numbers in the lower lobes represent the number of tumours and not their distribution within the lower lobe (this distribution is shown in both lateral views).

While prescribing the same dose to the target, most modalities had no problems adhering to the predefined objectives for OARs in most patients. In select cases, however, clear differences were noted between the modalities (Figure 3 A-F). For the oesophagus and the spinal cord, given the relatively peripheral location of the tumours, none of the plans exceeded the predefined dose constraints. However, for the DSP and IMIT plans, the D_{mean} and $D_{0.03\text{cc}}$ to these organs decreased significantly by more than 50% compared to IMRT ($p\leq 0.001$ for all values). For VMAT, the $D_{0.03\text{cc}}$ to the spinal cord was on average 3 Gy higher than for IMRT ($p=0.006$). For the heart, the D_{mean} was significantly lower for

Figure 2: Comparison of dose distribution of intensity-modulated radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), Cyberknife, Double Scattered Proton (DSP) and Intensity-Modulated Carbon-Ion (IMIT) plans.

Table 1: Dose volume metrics (with SD) after rescaling to 99% of the CTV receiving 60 Gy.

	Measure	IMRT	VMAT	Cyberknife	DSP	IMIT
CTV	D _{mean} (Gy)	65.1 (1.3)	65.7 (1.7)	68.1 (1.0)*	63.6 (1.5)*	63.1 (0.44)*
	D _{2%} (Gy)	70.6 (2.8)	70.3 (2.8)	72.9 (1.5)*	67.4 (3.1)*	66.6 (1.1)*
	D _{98%} (Gy)	60.3 (0.14)	60.5 (0.31)*	60.7 (0.35)*	60.3 (0.14)	60.2 (0.052)
	CN _{50%}	0.065 (0.026)	0.081 (0.026)*	0.11 (0.021)*	0.047 (0.024)*	0.11 (0.036)*
	CN _{80%}	0.18 (0.06)	0.22 (0.054)*	0.22 (0.038)*	0.093 (0.041)*	0.21 (0.056)*
	CN _{95%}	0.29 (0.081)	0.34 (0.07)*	0.32 (0.051)*	0.16 (0.062)*	0.28 (0.065)
Oesophagus	D _{mean} (Gy)	3.1 (1.5)	2.3 (1.1)*	2.7 (1.6)	0.41 (0.94)*	0.53 (0.75)*
	D _{0.03cc} (Gy)	14.5 (6.8)	11.1 (4.5)*	8.9 (5.5)*	6.2 (10.5)*	5.5 (8.2)*
Heart	D _{mean} (Gy)	1.2 (1.4)	0.91 (1.2)*	2.4 (1.8)*	0.083 (0.21)*	0.049 (0.097)*
	D _{0.03cc} (Gy)	10.6 (11.5)	8.1 (8.4)*	11.8 (5.8)	12.5 (18.2)	4.8 (7.6)*
Lungs-GTV	D _{mean} (Gy)	5.3 (1.9)	4.6 (1.9)*	4.9 (2.5)	4.8 (2.0)	2.8 (1.4)*
	V _{20Gy} (%)	8.1 (3.5)	6.7 (3.4)*	5.4 (3.8)*	9.7 (3.9)*	5.3 (2.8)*
	V _{5Gy} (%)	22.8 (7.5)	19.5 (7.3)*	24.3 (12.1)	13.9 (6.0)*	9.4 (4.2)*
	Ipsilateral V _{20Gy} (%)	16.4 (7.7)	13.5 (6.9)*	10.8 (7.1)*	19.6 (8.1)*	10.5 (4.9)*
	V _{5Gy} (%)	37.2 (13.3)	35.1 (13.2)*	41.1 (18.6)	28.1 (12.0)*	18.8 (8.0)*
	Contralateral V _{5Gy} (%)	9.9 (6.1)	4.9 (5.2)*	8.3 (9.1)	0.018 (0.064)*	0.14 (0.52)*
Mediastinal structures	D _{mean} (Gy)	2.6 (1.0)	2.1 (0.77)*	3.0 (1.5)	0.77 (0.64)*	0.4 (0.24)*
	D _{0.03cc} (Gy)	31.7 (11.6)	27.4 (9.9)*	27.4 (12.4)*	48.1 (18.4)*	32.9 (13.5)
Spinal cord	D _{0.03cc} (Gy)	9.7 (4.0)	13.1 (6.8)*	7.7 (5.7)*	3.7 (10.4)*	2.8 (3.2)*
Chest wall	D _{mean} (Gy)	7.3 (3.2)	5.9 (2.8)*	5.8 (3.2)*	6.2 (3.4)*	3.3 (1.8)*
	D _{0.03cc} (Gy)	52.5 (12.3)	51.0 (13.8)	52.9 (19.3)	64.5 (7.5)*	54.2 (13.3)*
	V _{32.5Gy} (cm ³)	36.2 (29.7)	26.5 (26.1)*	23.6 (23.0)*	62.8 (25.9)*	17.2 (15.0)*
	D _{mean} (Gy)	11.1 (3.3)	8.9 (3.1)*	8.4 (3.7)*	10.2 (5.3)	5.4 (2.8)*
Ribs	D _{0.03cc} (Gy)	51.2 (12.5)	47.3 (14.7)*	51.0 (19.9)	63.3 (7.6)*	52.8 (13.7)*

* = significant ($p < 0.01$); two-sided pairwise Wilcoxon test against IMRT, marked red if statistically significantly higher, green if lower. Abbreviations: CTV = clinical target volume, CN_{x%} = conformity number for the CTV for x% of the prescribed dose, SD = standard deviation, D_{mean} = mean dose, D_{2%} = minimum dose to 'hottest' 2% of the volume, D_{0.03cc} = dose to the 'hottest' 0.03cc, V_{xGy} = percentage of the volume receiving xGy or more

VMAT, DSP, and IMIT compared to IMRT, but was higher with CyberKnife. Heart D_{0.03cc} decreased by 55% and 24% for IMIT and VMAT, respectively ($p < 0.001$ for both modalities). The mean lung dose (MLD) was significantly lower for VMAT and IMIT compared to IMRT (relative difference 13% and 47%, respectively, $p < 0.001$ for both), even though the mean absolute difference was modest. DSP occasionally resulted in a larger volume of the ipsilateral lung receiving 20 Gy or more (for example patients 9, 10, 11 and 20; Figure 3E), resulting in a higher mean V_{20Gy} (9.7% for DSP vs 8.1% for IMRT, $p = 0.008$). Nevertheless, the low dose parameter for the lung, the V_{5Gy}, compared favourably with the photon modalities, for both DSP and IMIT (decrease of 39% ($p < 0.001$) and 59% ($p < 0.001$) for DSP

and IMIT, respectively). The lung V_{5Gy} was also slightly, but statistically significantly, lower for VMAT when compared to IMRT ($p < 0.001$). Contralateral lung dose was essentially negligible for both particle therapy plans (mean V_{5Gy} of 0.018% for DSP and 0.14% for IMIT, compared with 9.9% for IMRT).

Due to predominantly peripheral tumour locations (CTV overlapped the chest wall in 13 patients), high D_{max} values were noted in the chest wall: in only 9/25 (36%) patients the $D_{0.03cc}$ was lower than the objective, for one or more of the modalities (Figure 3F). This problem was encountered mainly in the planning of particle therapy: the $D_{0.03cc}$ to the chest wall increased significantly for both particle therapies, mainly for DSP (23% higher than IMRT, constituting an absolute 12Gy increase in dose, $p < 0.001$). For all modalities, however, the mean dose to the chest wall decreased significantly compared to IMRT (19%, 21%, 15%, 55% lower for VMAT, Cyberknife, DSP and IMIT, respectively). The influence of CTV size on the dose to the lungs and mediastinal structures was assessed and compared for all modalities (refer to Supplementary Figure). The slope of the linear trendlines was comparable for most modalities, with the exception of the Cyberknife, which was consistently the steepest. Therefore, Cyberknife may not be the first choice for larger tumours.

When the D_{max} to the chest wall or ribs was considered dose limiting, dose escalation was rarely possible using the DSP technique. Out of all DSP plans, the dose could be increased for only one patient (by 4%), compared to 29, 42, 33 and 25% of the cases planned with IMRT, VMAT, Cyberknife and IMIT, respectively. 'Ignoring' the dose to the chest wall and ribs enabled dose escalation to an MTD for 75, 96, 92, 42 and 71% of the patients for IMRT, VMAT, Cyberknife, DSP and IMIT, respectively, and dose escalation with all modalities was possible in a third of all patients ($N=8$; Table 2). In the remaining patients, the $D_{0.03cc}$ to the mediastinum hampered dose escalation in 15 patients when using DSP, and the dose to a cardiac device prohibited escalation in another patient when using IMRT.

In those 8 patients in whom dose escalation was performed, the primary dose-limiting organ was again the mediastinum (for 7 of the 8 patients, the MTD was first reached using DSP). The mean MTD to the CTV ranged widely, from 98Gy for DSP to 205Gy using Cyberknife. These mean MTDs for DSP and Cyberknife did not statistically significantly differ from the mean MTD of 133Gy reached with IMRT. Similarly, the differences in mean dose to all OARs did not reach statistical significance.

DISCUSSION

Several *in silico* planning studies are available in the literature comparing a type of stereotactic photon treatment with either carbon-ion or proton treatment for stage I NSCLC^{9-11,17}. However, the current international planning study is the largest *in silico* study to date and the first to compare multiple photon-based stereotactic radiotherapy plans (IMRT, VMAT and Cyberknife) with each other and with multiple particle therapy plans (DSP, IMIT) for early stage NSCLC.

Figure 3A-F

Figure 3A-F: Comparison of dose to the organ at risk (OAR) per patient for each modality, sorted by lowest to highest IMRT dose. Please note that the patient numbers do not correspond between the figures. The constraint or objective used for treatment planning is displayed as a red dashed line. Abbreviations: $D_{0.03cc}$ = minimum dose to the 'hottest' 0.03cc, V_{20Gy} = percentage receiving 20Gy.

In general, most OAR doses could be reduced using particles with IMIT offering the greatest benefit. However, VMAT and Cyberknife also allowed for reduced doses to most OARs compared with IMRT. Although DSP achieved the lowest mean oesophageal dose among all modalities, DSP performed worst for several important OARs, including the lung V_{20Gy} and D_{max} to the chest wall and mediastinal structures, negatively impacting on the dose escalate possibility. This is likely the result of the mostly two-beam set-up of the DSP plans, entailing higher proton beam entry doses and a loss of conformality, and these doses likely would have been reduced if 3 or 4 field plans had been utilised. Furthermore, it may well be possible to further reduce these D_{max} and other OAR doses using pencil beam scanning (PBS) and intensity-modulated proton therapy, but this was beyond the scope of the comparative *in silico* study¹⁸. Conversely, the beam set-up and the finite range of the proton beams resulted in less low dose spillage and thus the lowest V_{5Gy} of the contralateral lung, which, together with the D_{mean} of the contralateral lung have been linked to the incidence of radiation pneumonitis in several studies¹⁹⁻²¹. The mean and maximum doses to the heart were also lowest using particles, which is favourable when attempting to decrease cardiovascular events and deaths in the long-term²². Even though the heart dose was considered less relevant for lung cancer patients, recently improved outcome rates have turned the radiation-associated heart disease into a relevant outcome with multiple recent studies demonstrating this side-effect to occur earlier than previously assumed in patients with locally advanced NSCLC^{23,24}. For

Table 2: Dose volume metrics (with SD) for the eight patients for whom dose escalation to a maximum tolerated dose (MTD) was possible with all modalities.

		IMRT	VMAT	Cyberknife	DSP	IMIT
CTV	D _{mean} (Gy)	133.4 (29.2)	146.1 (40.7)	204.9 (51.8)	98.0 (42.7)	180.9 (132.2)
	D _{2%} (Gy)	144.2 (30.0)	156.2 (43.1)	221.8 (60.3)	103.1 (48.2)	191.2 (138.9)
	D _{98%} (Gy)	123.9 (27.3)	134.4 (37.5)	182.2 (46.9)	93.4 (38.6)	172.3 (125.4)
	CN _{50%}	0.061 (0.025)	0.075 (0.024)	0.1 (0.023)	0.044 (0.018)	0.099 (0.033)
	CN _{80%}	0.17 (0.058)	0.21 (0.053)	0.2 (0.04)	0.1 (0.04)	0.19 (0.054)
	CN _{95%}	0.27 (0.074)	0.32 (0.07)	0.3 (0.055)	0.17 (0.056)	0.27 (0.068)
Oesophagus	D _{mean} (Gy)	4.4 (2.2)	3.9 (1.4)	5.8 (3.3)	0.44 (0.94)	1.0 (1.1)
	D _{0.03cc} (Gy)	21.8 (8.6)	19.4 (2.7)	19.9 (6.7)	7.8 (13.1)	8.4 (8.6)
Heart	D _{mean} (Gy)	2.4 (2.6)	2.4 (3.0)	6.4 (3.7)	<0.01 (0.014)	0.091 (0.12)
	D _{0.03cc} (Gy)	17.9 (17.3)	15.6 (15.9)	32.2 (6.1)	5.9 (8.9)	8.5 (12.3)
Lungs-GTV	D _{mean} (Gy)	9.6 (3.6)	9.2 (4.8)	12.4 (5.1)	7.4 (5.7)	8.0 (10.4)
	V _{20Gy} (%)	13.1 (5.3)	11.9 (6.2)	16.1 (7.9)	11.4 (5.7)	7.6 (5.2)
Ipsilateral	V _{5Gy} (%)	32.5 (11.3)	34.3 (12.6)	44.1 (15.9)	16.1 (8.8)	12.5 (6.7)
	V _{20Gy} (%)	24.9 (10.1)	22.7 (11.1)	29.2 (14.3)	21.6 (10.1)	14.4 (9.4)
Contralateral	V _{5Gy} (%)	45.1 (14.7)	43.6 (15.3)	61.1 (21.6)	30.5 (15.6)	22.8 (11.4)
	V _{5Gy} (%)	19.2 (8.6)	24.3 (10.2)	26.5 (14.8)	<0.01 (<0.01)	1.3 (1.8)
Mediastinal structures	D _{mean} (Gy)	4.2 (1.4)	3.9 (1.5)	7.1 (2.8)	0.36 (0.27)	0.54 (0.26)
	D _{0.03cc} (Gy)	41.0 (<0.01)	38.7 (6.4)	41.0 (0.011)	41.0 (<0.01)	41.0 (0.013)
Spinal cord	D _{0.03cc} (Gy)	18.0 (8.2)	20.7 (7.0)	16.6 (5.8)	2.7 (7.5)	2.8 (2.9)

Abbreviations: CTV = clinical target volume, CN_{x%} = conformity number for the CTV for x% of the prescribed dose, D_{mean} = mean dose, D_{2%} = minimum dose to 'hottest' 2% of the volume, D_{0.03cc} = dose to the 'hottest' 0.03cc, V_{xGy} = percentage of the volume receiving xGy or more

stage I NSCLC patients, who can potentially be long-term survivors, minimising the dose to the heart is of even greater importance. Stam *et al.*²⁵ recently report that in particular doses to the upper region of the heart (atria and vessels) are significantly associated with non-cancer death in early stage NSCLC patients having undergone SABR.

For this *in silico* planning study, datasets of patients who have actually been treated with photon SABR were used for treatment planning. Therefore, most tumours were located peripherally in the lung, as no one consensus for the delivery of SABR for centrally located tumours in close proximity to the main airways, the heart or great vessels, or the oesophagus exists²⁶⁻³⁰. The ongoing European Organisation for Research and Treatment of Cancer (EORTC) sponsored 22113-08113-LungTech study is evaluating the safety and effectiveness of photon SABR in patients with inoperable and centrally located early stage NSCLC³¹. For small, peripherally located tumours, however, the risk of serious toxicity with SABR is low as the tumours are usually located far away from critical tissue³².

Hence, particle therapy is not likely to be advantageous for the unselected patient with a small, peripheral lesion. Any potential clinical benefits are likely to be small and not likely to outweigh the extra treatment costs for state-of-the-art particle treatment that has limited availability. As such, patients with tumours located near the thoracic wall may be best served with the modern VMAT and Cyberknife techniques, as DSP might even be disadvantageous for some patients due to the high maximum doses in the chest wall and mediastinal structures.

Correspondingly, the Particle Therapy Co-operative Group (PTCOG) concluded in its consensus statement on proton therapy in lung cancer that it rarely improves dosimetry in a clinically meaningful way in patients with small peripheral lesions. They attribute this to a lower stopping power of the protons in lung parenchyma consequently resulting in a higher exit dose³³. The PTCOG suggests that stereotactic radiotherapy with protons or carbon ions may be more clinically beneficial in patients with a centrally located tumour (where protons have mediastinal soft tissue to stop in), a large primary tumour (>5cm), multiple tumours or in case of re-irradiation^{33,34}. These patients would otherwise be subjected to daily fractionated radiotherapy or be unable to receive radiotherapy. Further investigation into these subpopulations of patients with early stage NSCLC is warranted³⁵.

Our study has several limitations. First, even though tumour motion and anatomical variations are of greater influence in particle than in photon radiotherapy due to the finite range of charged particles, we did not take tumour motion into account: this was beyond the scope of our *in silico* trial. If motion amplitudes and range uncertainties were to be incorporated in the proton and carbon-ion plans, the uncertainty margins would even have been larger, especially for smaller tumours of the lower lobes⁹. This could have decreased the advantage of the particle treatments observed in this study. Conversely, a greater relative benefit might have been seen with CyberKnife planning since reduced PTV margins can be used as tumour motion is taken into account by tumour tracking.

Second, despite the ROCOCO planning protocol being adhered to, the participating centres were free to choose beam set-up and optimisation criteria based on their own in-house treatment protocols. This may have led to relevant differences in the treatment planning results. To determine the influence of rescaling the dose, the analyses were repeated without rescaling, thus comparing the original plans (refer to Supplementary Table). This would not have changed the conclusions of our study.

Another limitation is the clinical applicability of IMIT for lung cancer. Even though from a dosimetric standpoint IMIT might be superior to conformal photon techniques, uncertainties regarding dose distribution and radiobiological effectiveness of carbon

ions suggest a need for caution. Carbon ions are known for their high linear energy transfer and the resulting radiobiological advantage, mainly in the Bragg peak region. However, for high doses, this effect is currently not well characterised and is the subject of ongoing research ³⁶. Furthermore, the availability of intensity modulated carbon ions delivered with a gantry (as used for treatment planning in the current study) is limited to the Heidelberg Ion Therapy Center in Heidelberg, the partner centre of UHM.

Fourth, despite the relative differences between the doses to the OAR often being substantial, the absolute differences were relatively modest and resulting clinical significance unclear. Choosing a more expensive or less widely available modality, such as proton or carbon-ion therapy, can only be clinically worthwhile and cost-effective if the decrease in OAR dose actually results in significantly less (serious) toxicities and/or improved tumour control. For these new, costlier and less widely available techniques, the model based approach may help to carefully select patients who will likely benefit from the dose reductions achieved with particles and results feed into the rapid learning approach ³⁵. A step further towards personalised radiotherapy involves incorporating NTCP models in decision support systems, ensuring all dosimetric, patient, biological and other known factors influencing disease outcome and toxicities are taken into account. Prospective data registration and evaluation, *e.g.*, in the rapid learning approach, to validate and update the generated multifactorial NTCP models is essential for accurate patient selection.

CONCLUSION

In summary, the doses to the OARs for peripheral stage I NSCLC were lowest using carbon ions. Differences were often modest, however, and the clinical relevance of the reduction in dose to the OAR is unclear. In case of DSP, while mean and low dose irradiation was uniformly reduced, the maximum doses to the chest wall and ribs were significantly higher than with IMRT. VMAT and Cyberknife allowed for dose sparing of several OARs compared with IMRT. Therefore, the incremental additional benefit of particle beam therapy for stage I NSCLC may not be the most relevant indication for proton therapy or carbon therapy. However, for central, large ³⁷ or recurrent (previously irradiated) tumours, particle therapy could be beneficial and warrants additional investigation.

Supplementary table: Dose volume metrics (with SD) of the original planning data, without rescaling.

		IMRT	VMAT	Cyberknife	DSP	IMIT
CTV	D _{mean} (Gy)	69.2 (3.1)	71.0 (2.7)*	69.6 (1.3)	63.1 (2.9)*	65.8 (0.85)*
	D _{2%} (Gy)	75.0 (3.6)	76.0 (3.3)	74.5 (0.48)	66.9 (3.6)*	69.5 (1.3)*
	D _{98%} (Gy)	64.1 (3.0)	65.4 (3.0)	62.1 (1.5)*	59.9 (2.6)*	62.9 (0.78)
PTV	D _{mean} (Gy)	66.7 (2.4)	67.4 (1.5)	67.6 (0.87)	62.7 (2.6)*	65.1 (0.75)*
	D _{2%} (Gy)	74.2 (3.5)	75.3 (3.1)	74.1 (0.5)	66.8 (3.4)*	68.9 (1.1)*
	D _{98%} (Gy)	60.7 (1.6)	58.6 (1.2)*	60.7 (0.42)	57.7 (2.8)*	61.0 (0.84)
Oesophagus	D _{mean} (Gy)	3.3 (1.6)	2.5 (1.1)*	2.8 (1.7)	0.4 (0.92)*	0.55 (0.78)*
	D _{0.03cc} (Gy)	15.4 (7.2)	11.9 (4.6)*	9.1 (5.6)*	6.2 (10.4)*	5.8 (8.5)*
Heart	D _{mean} (Gy)	1.3 (1.4)	0.97 (1.3)*	2.4 (1.8)*	0.085 (0.22)*	0.05 (0.1)*
	D _{0.03cc} (Gy)	11.2 (12.3)	8.7 (9.0)*	12.0 (5.9)	12.5 (18.4)	5.0 (8.0)*
Lungs-GTV	D _{mean} (Gy)	5.6 (2.0)	5.0 (2.0)*	5.1 (2.6)	4.8 (2.0)*	3.0 (1.5)*
	V _{20Gy} (%)	8.6 (3.6)	7.2 (3.6)*	5.5 (3.9)*	9.7 (4.0)	5.5 (2.9)*
	V _{5Gy} (%)	23.7 (7.7)	20.5 (7.3)*	24.8 (12.4)	13.9 (6.1)*	9.5 (4.3)*
Ipsilateral	V _{20Gy} (%)	17.4 (7.6)	14.6 (7.1)*	11.1 (7.3)*	19.5 (8.2)	10.9 (5.0)*
	V _{5Gy} (%)	37.9 (13.3)	36.0 (13.1)*	41.7 (18.8)	28.1 (12.1)*	19.0 (8.1)*
Contralateral	V _{5Gy} (%)	11.1 (6.2)	5.9 (5.4)*	8.7 (9.5)	0.018 (0.062)*	0.16 (0.56)*
Mediastinal structures	D _{mean} (Gy)	2.8 (1.1)	2.2 (0.77)*	3.1 (1.5)	0.77 (0.63)*	0.42 (0.25)*
	D _{0.03cc} (Gy)	33.7 (12.3)	29.6 (10.6)*	28.1 (12.8)*	47.9 (18.5)*	34.4 (14.3)
Spinal cord	D _{0.03cc} (Gy)	10.2 (4.3)	14.1 (7.0)*	7.9 (5.8)*	3.6 (9.9)*	2.9 (3.3)*
Chest wall	D _{mean} (Gy)	7.7 (3.1)	6.3 (2.8)*	5.9 (3.3)*	6.1 (3.5)*	3.4 (1.9)*
	D _{0.03cc} (Gy)	55.4 (11.4)	54.7 (13.5)	53.9 (19.3)	64.0 (7.6)*	56.6 (13.9)
Ribs	D _{mean} (Gy)	11.8 (3.2)	9.6 (3.1)*	8.6 (3.8)*	10.1 (5.1)	5.6 (2.9)*
	D _{0.03cc} (Gy)	54.0 (11.7)	50.6 (14.4)*	51.9 (19.9)	62.8 (7.7)*	55.1 (14.3)

* = significant (p<0.01); two-sided pairwise Wilcoxon test against IMRT, marked red if statistically significantly higher, green if lower. Abbreviations: CTV = clinical target volume, PTV = planning target volume, SD = standard deviation, D_{mean} = mean dose, D_{2%} = minimum dose to 'hottest' 2% of the volume, D_{0.03cc} = dose to the 'hottest' 0.03cc, V_{xGy} = percentage of the volume receiving xGy or more.

Supplementary Figure: Scatter diagrams comparing clinical target volume (CTV, cc) with: A) mean lung dose (MLD), B) percentage of the lungs receiving 20Gy or more (V_{20Gy}), C) $V_{50\%}$ and D) minimum dose to the 'hottest' 0.03cc ($D_{0.03cc}$) of the PRV of the mediastinal structures.

REFERENCES

1. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ, Senan S. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2010;28(35):5153-5159.
2. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2008;70(3):685-692.
3. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *International journal of radiation oncology, biology, physics*. 2012;83(1):348-353.
4. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637.
5. van der Voort van Zyp NC, Prevost JB, van der Holt B, et al. Quality of life after stereotactic radiotherapy for stage I non-small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 2010;77(1):31-37.
6. Wink KC, Roelofs E, Solberg T, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Frontiers in oncology*. 2014;4:292.
7. Yamamoto N, Miyamoto T, Nakajima M, et al. A Dose Escalation Clinical Trial of Single-Fraction Carbon Ion Radiotherapy for Peripheral Stage I Non-Small Cell Lung Cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2017;12(4):673-680.
8. Roelofs E, Engelsman M, Rasch C, et al. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2012;7(1):165-176.
9. Anderle K, Stroom J, Pimentel N, Greco C, Durante M, Graeff C. In silico comparison of photons versus carbon ions in single fraction therapy of lung cancer. *Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics*. 2016;32(9):1118-1123.
10. Ebara T, Shimada H, Kawamura H, et al. Dosimetric analysis between carbon ion radiotherapy and stereotactic body radiotherapy in stage I lung cancer. *Anticancer research*. 2014;34(9):5099-5104.
11. Macdonald OK, Kruse JJ, Miller JM, et al. Proton beam radiotherapy versus three-dimensional conformal stereotactic body radiotherapy in primary peripheral, early-stage non-small-cell lung carcinoma: a comparative dosimetric analysis. *International journal of radiation oncology, biology, physics*. 2009;75(3):950-958.
12. Hoppe BS, Huh S, Flampouri S, et al. Double-scattered proton-based stereotactic body radiotherapy for stage I lung cancer: a dosimetric comparison with photon-based stereotactic body radiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2010;97(3):425-430.
13. Eekers DB, Roelofs E, Jelen U, et al. Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016.

14. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(30):4833-4839.
15. Shaikh T, Turaka A. Predictors and management of chest wall toxicity after lung stereotactic body radiotherapy. *Cancer treatment reviews*. 2014;40(10):1215-1220.
16. van't Riet A, Mak AC, Moerland MA, Elders LH, van der Zee W. A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: application to the prostate. *International journal of radiation oncology, biology, physics*. 1997;37(3):731-736.
17. Hoppe BS, Flampouri S, Henderson RH, et al. Proton therapy with concurrent chemotherapy for non-small-cell lung cancer: technique and early results. *Clinical lung cancer*. 2012;13(5):352-358.
18. Lin L, Kang M, Huang S, et al. Beam-specific planning target volumes incorporating 4D CT for pencil beam scanning proton therapy of thoracic tumors. *Journal of applied clinical medical physics*. 2015;16(6):281-292.
19. Ong CL, Palma D, Verbakel WF, Slotman BJ, Senan S. Treatment of large stage I-II lung tumors using stereotactic body radiotherapy (SBRT): planning considerations and early toxicity. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2010;97(3):431-436.
20. Khalil AA, Hoffmann L, Moeller DS, Farr KP, Knap MM. New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy. *Acta oncologica*. 2015;54(9):1343-1349.
21. Bongers EM, Botticella A, Palma DA, et al. Predictive parameters of symptomatic radiation pneumonitis following stereotactic or hypofractionated radiotherapy delivered using volumetric modulated arcs. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2013;109(1):95-99.
22. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *The New England journal of medicine*. 2013;368(11):987-998.
23. Wang K, Eblan MJ, Deal AM, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;JCO2016700229.
24. Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;35(13):1395-1402.
25. Stam B, Peulen H, Guckenberger M, et al. Dose to heart substructures is associated with non-cancer death after SBRT in stage I-II NSCLC patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2017;123(3):370-375.
26. Vansteenkiste J, Crino L, Doooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2014;25(8):1462-1474.
27. Chang JY, Bezjak A, Mornex F, Committee IART. Stereotactic ablative radiotherapy for centrally located early stage non-small-cell lung cancer: what we have learned. *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer*. 2015;10(4):577-585.
28. Schneider BJ, Daly ME, Kennedy EB, et al. Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American

- Society for Radiation Oncology Evidence-Based Guideline. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2017;JCO2017749671.
29. Guckenberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2017;124(1):11-17.
 30. De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2017;124(1):1-10.
 31. Adebahr S, Collette S, Shash E, et al. LungTech, an EORTC Phase II trial of stereotactic body radiotherapy for centrally located lung tumours: a clinical perspective. *The British journal of radiology*. 2015;88(1051):20150036.
 32. Roach MC, Videtic GM, Bradley JD, Committee IART. Treatment of Peripheral Non-Small Cell Lung Carcinoma with Stereotactic Body Radiation Therapy. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2015;10(9):1261-1267.
 33. Chang JY, Jabbour SK, De Ruysscher D, et al. Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. *International journal of radiation oncology, biology, physics*. 2016;95(1):505-516.
 34. Grant JD, Chang JY. Proton-based stereotactic ablative radiotherapy in early-stage non-small-cell lung cancer. *BioMed research international*. 2014;2014:389048.
 35. Widder J, van der Schaaf A, Lambin P, et al. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. *International journal of radiation oncology, biology, physics*. 2016;95(1):30-36.
 36. Friedrich T, Scholz U, Durante M, Scholz M. RBE of ion beams in hypofractionated radiotherapy (SBRT). *Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics*. 2014;30(5):588-591.
 37. Verma V, Shostrom VK, Zhen W, et al. Influence of Fractionation Scheme and Tumor Location on Toxicities After Stereotactic Body Radiation Therapy for Large (≥ 5 cm) Non-Small Cell Lung Cancer: A Multi-institutional Analysis. *International journal of radiation oncology, biology, physics*. 2017;97(4):778-785.

CHAPTER 7

Photons or protons for re-irradiation in (non-)small cell lung cancer? Results of the multicentric ROCOCO *in silico* study

Esther G.C. Troost, Krista C.J. Wink, Erik Roelofs, Charles B. Simone II, Sebastian Makocki, Steffen Löck, Peter van Kollenburg, David Dechambre, Andre W.H. Minken, Judith van der Stoep, Stephen Avery, Nicolas Jansen, Timothy Solberg, Johan Bussink, Dirk de Ruyscher

Submitted

ABSTRACT

Purpose

Locally recurrent disease is of increasing concern in (non-)small cell lung cancer patients [(N)SCLC]. Local re-irradiation with photons or particles may be of benefit to these patients. In this multicentre *in silico* trial performed within the Radiation Oncology Collaborative Comparison (ROCOCO) consortium, the doses to the target volumes and organs at risk (OARs) were compared when using several photon and proton techniques in patients with recurrent localized lung cancer scheduled to undergo re-irradiation.

Methods

Twenty-four consecutive patients with a second primary (N)SCLC or recurrent disease after curative-intent, standard fractionated radio(chemo)therapy were included in this study. The target volumes and OARs were centrally contoured and distributed to the participating ROCOCO sites. Remaining doses to the OARs were calculated on an individual patient's basis. Treatment planning was performed by the participating site using the clinical treatment planning system and associated beam characteristics.

Results

Treatment plans for all modalities (5 photon and 2 proton plans per patient) were available for 22 patients (N=154 plans). 3D-conformal photon therapy and double-scattered proton therapy delivered significantly lower doses to the target volumes. The highly conformal techniques, *i.e.*, IMRT, VMAT, CyberKnife, TomoTherapy and IMPT, reached the highest doses in the target volumes. Of these, IMPT was able to statistically significantly decrease the radiation doses to the OARs.

Conclusion

Highly conformal photon and proton beam techniques enable high-dose re-irradiation of the target volume. They, however, significantly differ in the dose deposited in the OARs. The therapeutic options, *i.e.*, re-irradiation or systemic therapy, need to be carefully weighed and discussed with the patients.

INTRODUCTION

Patients with lung cancer may develop a second primary lung tumour or recurrent disease after primary radiotherapy. In fact, approximately one-quarter of all patients treated for lung cancer will subsequently suffer from a second primary lung cancer and 30-50% of patients with locally advanced non-small cell lung cancer (NSCLC) treated with definitive radiation therapy and chemotherapy will have a locoregional failure¹. In cases of isolated localized recurrences or new primary lung cancers, re-irradiation can be considered and may represent the only chance of cure in these patient populations^{2,3}.

Due to the physical advantages of ions, particle therapy (proton and carbon-ion therapy) has the potential to inflict maximum damage on tumours with limited collateral damage to neighbouring healthy tissues. Previous publications on the use of particle beam therapy for lung cancer patients have shown encouraging results⁴. With more advanced techniques such as particle therapy, mitigating or compensating for intrafractional movement of the target volume and for any interfractional anatomical changes are critical for (N)SCLC patients^{5,6}. In order to avoid detrimental acute and chronic toxicity, doses to critical organs such as the lungs, heart, large blood vessels, proximal bronchi, oesophagus and spinal cord, have to be considered thoroughly in the setting of a re-irradiation. The normal tissue dose constraints for re-irradiation should be calculated on an individual patient's basis accounting for the doses previously received by organs at risk (OARs) from the initial irradiation course⁷. Patients with recurrent disease may benefit from particle therapy. Conversely, conventional photon-based radiotherapy has also improved over the recent years. With modern Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), high-dose, curative-intent re-irradiation of the recurrent tumour is feasible while also resulting in relatively low doses to the surrounding OARs. Modern photon and particle therapy, therefore, allow for a decreased risk of radiation-induced complications and an increased likelihood of local control and ultimately cure.

To date, it is not clear to what extent patients with a second primary lung tumour or recurrent disease benefit from particle therapy compared to modern photon therapy. Therefore, it is necessary to define the possible advantages that may exist in particle therapy and whether they can outweigh the considerably higher (upfront) cost. Since comparison of treatment modalities cannot be achieved for an individual patient, we conducted a series of *in silico* trials for different disease entities and therapeutic settings⁸⁻¹¹. In this study, we present the data of a multicentre *in silico* trial performed within the Radiation Oncology Collaborative Comparison (ROCOCO) consortium, comparing the dose to the target volume and the surrounding OARs using several photon and proton techniques in patients with recurrent localized lung cancer scheduled to undergo re-irradiation.

PATIENTS AND METHODS

Patients

Twenty-four consecutive patients with a second primary (non-)small cell lung cancer or recurrent disease after curative-intent, standard fractionated radio(chemo)therapy, treated at MAASTRO clinic (Department of Radiotherapy, Maastricht University Medical Center+, The Netherlands) between 2006 and 2014, were included in this *in silico* planning study. The study was approved by the Institutional Review Board of MAASTRO clinic.

Delineation of target volumes and organs at risk

The tumour volumes and OARs were centrally (re-)contoured in the mid-ventilation phase of a four-dimensional ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (4D-FDG-PET-CT) scan (CT in soft tissue and lung window-width/window-level-setting) with patients positioned supine with their arms above the head using an arm-rest and leg support. The CT data consisted of non-overlapping 2-3 mm slices with a maximum image resolution of 512×512 mm. The CT encompassed the entire thorax in order to obtain accurate dose-volume histogram data of the intrathoracic OARs. The image datasets and delineated contours were made available to all participating sites guaranteeing uniformity.

The gross tumour volume (GTV) included all detectable gross disease, the clinical target volume (CTV) comprised the GTV with a 5 mm-margin encompassing microscopic tumour extension, subsequently corrected for anatomical boundaries. The planning target volume (PTV) was constructed using an isotropic 10 mm margin around the CTV. For evaluation purposes, the PTV was clipped 3 mm below the outer body contour to compensate for the photon build-up effect. In this setting of re-irradiation, a wide range of OARs was contoured to enable calculation of doses to these OARs and the remaining body. We contoured the ipsilateral and contralateral lung separately as well as together, subtracting the GTV for dose evaluation. The heart, spinal cord, oesophagus, trachea, main bronchi, bilateral brachial plexus, ribs and chest wall were also contoured. A 'mediastinal envelope' structure was also contoured that compromised the heart/pericardium, large vessels, trachea, main bronchi and oesophagus, and was expanded to a planning risk volume (PRV) using a margin of 5 mm to correct for setup inaccuracies (PRV mediastinal envelope)¹¹.

Treatment planning

For each patient, five photon plans (3D-conformal radiotherapy [3D-CRT]; IMRT; VMAT; TomoTherapy; and CyberKnife), and two proton plans (double scattered proton therapy

[DSPT]; and intensity modulated proton therapy [IMPT]) were calculated at MAASTRO clinic (VMAT), University Hospital Carl Gustav Carus Dresden (3D-CRT and DSPT), Radboud University Medical Center (IMRT), the Centre Hospitalier Universitaire de Liège (CyberKnife), Radiotherapiegroup Deventer (TomoTherapy), and the Hospital of the University of Pennsylvania (IMPT), respectively.

Treatment planning was performed according to protocol, keeping within the tolerance doses of the OARs. Based on the delivered dose during the individual patient's first treatment course and the interval between the first and second course of irradiation, individual OAR dose constraints were determined for each patient (Supplementary Table) using the dose and dose-volume constraints reported in Table 1. The remaining equivalent dose in 2 Gy fractions (EQD2) to the PTV was calculated for every patient, being at least 54 Gy in 1.8 Gy fractions. The following priorities were set for the objectives (numbered in order of decreasing importance): 1 = spinal cord, 2 = PRV mediastinal envelope, 3 = heart, 4 = brachial plexus, 5 = lungs, 6 = ribs and chest wall.

Each centre used their own, clinically commissioned treatment planning system assuring state-of-the-art dose calculations. The dose was prescribed to the given PTV. Planning objectives were in accordance with several multi-institutional trials (e.g. RTOG 0618 and RTOG 0236), where at least 99% of the PTV should receive at least 95% of the prescribed dose, and the maximum dose ($D_{\max}$) should not exceed 140%. According to the study protocol, the dose to the CTV was also evaluated.

Photons

The VMAT plans were created using Eclipse v. 11.0 (Varian Medical Systems, Palo Alto, CA). The plans generally consisted of two 180-degree arcs with energies of 10 MV. The 3D-CRT treatment plans were generated using 6 MV and 15 MV photons and the treatment planning system Oncentra OTP v. 4.3 (Elekta, Stockholm, Sweden). The step-and-shoot IMRT plans were calculated using Pinnacle v. 9.6 (Philips Radiation Oncology Systems, Fitchburg, WI). Five to seven (mainly equally spaced) 10 MV photon beams were employed, avoiding beam entrance through the contralateral lung. CyberKnife plans were created using Multiplan v. 5.2.1 (Accuray Inc., Sunnyvale, CA). The non-coplanar beam arrangement was chosen from a large set of predefined nodes (full-path). A maximum of three collimators were used and the collimator diameter was case dependent (usually ranging from 60 to 80% of the largest PTV diameter). TomoTherapy treatment plans were created using the Accuray Hi-Art Planning Station (v5.1.0.4, Accuray). The 6 MV helical TomoTherapy plans were calculated using a pitch of 0.287 and a 2.5 cm slit width modulated by 64 binary multileaf collimators.

Table 1: Organ at risk dose constraints used for calculating the possible remaining dose depending on the interval between first and second course of irradiation.

	Time between 2 irradiation series	Maximal summed dose (D_{max} ; Gy) in 2-Gy fractions	Maximal dose (D_{max} ; Gy) allowed for 2 nd radiation in 2-Gy fractions	Volume allowed more than the maximum dose in the second radiation plan
Spinal cord	0.75 -5 years	65	45	0,03 cc
	>5years	75	45	0,03 cc
Oesophagus	9 months or more	100	65	0,03 cc
Mediastinal envelope	9 months or more	110	70	0,03 cc
Trachea	9 months or more	110	70	0,03 cc
Brachial plexus*	9 months or more	85	60	0,03 cc
	Time between 2 irradiation series	Mean summed dose (D_{mean} in Gy)	Mean dose 2 nd irradiation (Gy)	
Lungs	9 months or more	22	18 V20Gy<50%	
Contralateral lung			V5Gy <60%	
Heart	9 months or more	70	46	

* Only take constraint into account for patients where the brachial plexus is contoured (this automatically means that the plexus is close to the PTV). For the other patients the plexus should be avoided as much as possible.

Abbreviations: PRV, planning risk volume; GTV, gross tumour volume; D_{max} , maximum dose; D_{mean} , mean dose; V_{XXGy} , volume of organ at risk (in %) receiving a dose of XX Gy.

Protons

The DSPT plans were calculated using Oncentra XiO® v. 5.00.01 (Elekta) taking into account an RBE of 1.1 and 2-3 beams of 100-226.7 MeV such that the contralateral lung and critical OARs were avoided as much as possible. For calculation of the IMPT plans, Eclipse v. 11.0 (Varian Medical Systems) was used. The field size was limited to 12 cm. Beam arrangements were chosen based on the path of least variation. Portals were designed to avoid OARs distal to the target. Plans with 2-3 fields were created as a trade-off between treatment time and target conformity. The energy-dependent spot size used in clinical practice was applied. For all proton plans, since the plans were calculated for the PTV as opposed to the CTV, no additional margins for robustness, range and positioning uncertainty were taken into account.

Data storage and analysis

The Multicentric *In Silico* Trials In Radiotherapy (MISTIR) framework was used for data storage and exchange. The participating ROCOCO partners downloaded the datasets from the MISTIR database to perform treatment planning. After completion of the treatment plans, the dose matrices were re-uploaded to the database in DICOM format (Digital Imaging and Communication in Medicine). The dose-volume metrics were extracted

and compared to the VMAT plans, which were considered as the 'gold standard'. Of the following parameters, the ones relevant for the CTV, PTV, and OAR were compared among the treatment plans: mean dose (D_{mean}); minimum dose to the 'hottest' 0.03 cc ($D_{0.03\text{cc}}$, near maximum dose), highest dose to 2% of the volume ($D_{2\%}$, near maximum dose); lowest dose to 99% of the volume ($D_{99\%}$, near minimum dose); volume of a structure receiving a radiation dose of xx Gy (V_{xxGy}) given in cc.

The evaluation of the results was based 1) on the original treatment plans, in which no target dose rescaling was performed, since both the remaining dose to the OARs for the individual patients and the doses achieved in the target volumes varied, and 2) on rescaling to the maximally tolerable dose achievable until the first OAR dose constraint was reached. Differences in dose-volume parameters were tested for statistical significance between VMAT and the other irradiation techniques using the paired Wilcoxon signed-rank test (R Statistics 3.3.2, R Foundation for Statistical Computing, Vienna). The p -values were corrected for multiple testing by the Bonferroni method, accounting for the 6 comparisons per dose-volume parameter. Two-sided tests were performed and p -values <0.05 were considered as statistically significant.

RESULTS

In total, 24 complete patient data sets including all treatment modalities were available for statistical analysis. For one of the 24 patients, an electron instead of a photon treatment plan was calculated for the 3D-CRT technique. For another patient, two identical IMPT plans were calculated but named differently. Therefore, across all techniques, only 22 treatment plans were available for analysis of the dose to the target volumes and OARs.

For all comparisons, VMAT plans served as reference. For the original plans without rescaling, compared to VMAT, the overall $D_{0.03\text{cc}}$ in the PTV was statistically significantly lower for 3D-CRT, IMRT, TomoTherapy and DSPT, similar for IMPT and significantly higher for CyberKnife (Table 2). The $D_{99\%}$ was similarly high for VMAT, IMRT, CyberKnife, TomoTherapy, and IMPT, and significantly lower for the 3D-CRT and DSPT treatment plans. For the CTV, the D_{mean} , $D_{99\%}$ and $D_{0.03\text{cc}}$ were significantly lower for the 3D-CRT and DSPT treatment plans.

For the overall radiation dose values to the OARs, clinically relevant differences were also observed (Table 2). In the 3D-CRT plans, which achieved lower doses to the CTV and PTV (see above), the reported doses to the spinal cord, oesophagus, mediastinal envelope, trachea, bronchi, lungs ($V_{5\text{Gy}}$) were significantly lower compared to VMAT. In the IMRT plans, the D_{mean} and $V_{20\text{Gy}}$ to the lungs and the D_{mean} to the heart were sta-

tistically significantly higher compared to the respective values for VMAT. CyberKnife, reaching the highest doses in the target volumes, deposited significantly higher doses in the oesophagus, mediastinal envelope, trachea, left bronchus ($D_{2\%}$), and lungs (D_{mean} and $V_{5\text{Gy}}$), whereas it achieved lower doses in the right bronchus. The TomoTherapy treatment plans largely resembled those of VMAT, although D_{mean} and $V_{5\text{Gy}}$ to the heart were statistically significantly higher than with VMAT. For DSPT, the target doses were not reached in most cases, even though multiple double-scattered proton beams were used. Consequently, and also due to the physical characteristics of protons, the doses to the OARs were in general lower compared to VMAT. This was true for all OARs evaluated,

Table 2: Median dose to target volumes and organs at risk delivered with the respective treatment modalities.

		VMAT	3D-CRT	IMRT	CYBER	TOMO	DSPT	IMPT
CTV	$D_{0.03\text{cc}}$	59,7	57,6**	58,8*	73,4**	55,8**	56,0**	60,3
	D_{mean}	55,4	53,3**	55,1	63,2*	53,8**	53,3**	57,0*
	$D_{99\%}$	52,9	44,8**	52,8	55,8	52,7	42,3**	53,5
PTV	$D_{0.03\text{cc}}$	60,7	58,1**	59,2*	73,4**	57,1**	56,2**	60,5
	D_{mean}	55,6	52,3**	54,9*	61,8	54,0*	53,3**	56,3
	$D_{99\%}$	51,3	39,4**	51,4	51,5	51,9	39,3**	51,4
Spinal cord	$D_{0.03\text{cc}}$	23,8	20,4*	24,2	14,3	21,1	18,9**	17,5**
Oesophagus	$D_{0.03\text{cc}}$	47,8	31,6*	44,8	43,0	47,7	34,0**	51,7
	D_{mean}	10,8	7,1*	12,2	11,7*	10,7	3,2**	8,1*
Mediastinal envelope	$D_{0.03\text{cc}}$	58,5	47,2**	57,8	66,9*	54,8	46,9**	57,5
Trachea	D_{mean}	10,7	6,3*	9,5	11,2**	10,0	2,5**	4,9
	$D_{0.03\text{cc}}$	45,7	31,0*	41,0	42,4	44,0	35,5*	44,2
Left bronchus	D_{mean}	16,9	15,7*	19,2	17,1	16,3	9,1**	10,4**
	$D_{2\%}$	35,9	33,3*	36,5	43,2*	40,7	24,7**	47,7
Right bronchus	D_{mean}	16,0	13,6*	12,6	12,1*	15,0	3,5*	11,4
	$D_{2\%}$	35,4	28,7*	24,1	23,2*	21,0	17,6*	33,7
Lungs	D_{mean}	6,2	6,0	6,4*	7,6*	7,0	3,7**	3,8**
	$V_{20\text{Gy}}$	8,7	9,6	11,1*	8,4	10,0	7,4	7,4*
	$V_{5\text{Gy}}$	33,8	25,3*	33,8	44,2*	38,7	13,5**	13,5**
Heart	D_{mean}	1,6	2,3	3,0*	3,6	3,4*	0,3**	0,37**
	$V_{20\text{Gy}}$	0,1	0,6	2,1	0,0	2,0	0,0	0,3
	$V_{5\text{Gy}}$	8,0	10,5	13,5	26,7	11,8*	1,7*	1,9*
Integral body	D_{mean}	4,4	4,0	4,9**	5,3**	5,1**	2,9**	2,3**

CTV, clinical target volume; PTV, planning target volume; $D_{0.03\text{cc}}$, minimum dose to the 'hottest' 0.03 cc; D_{mean} , mean dose to structure; $D_{2\%}$, highest dose to 2% of the volume; $D_{99\%}$, lowest dose to 99% of the volume; $V_{xx\text{Gy}}$, volume of a given structure receiving a radiation dose of xxGy. Outcomes are reported in Gy (dose) or percentage (volume).

* represents $p \leq 0.05$, ** $p \leq 0.001$, when compared to VMAT, respectively.

albeit to a varying extent. Using IMPT, lower doses to OARs were also achieved, even though sufficient target coverage was reached. Doses to the spinal cord, oesophagus, left bronchus (D_{mean}), lungs (D_{mean} and $V_{5\text{Gy}}$), and heart (D_{mean} and $V_{5\text{Gy}}$) were statistically significantly lower compared to VMAT. Overall, the mean dose to the integral body was significantly lower for both proton beam techniques, and higher using any of the conformal rotational photon techniques, again when compared to VMAT.

In order to compensate for different treatment planning techniques, the plans were re-scaled to maximally tolerable dose until the first OAR dose constraint was reached

Table 3. Median dose to target volumes and OARs after deploying re-scaling to the maximum tolerated dose to the first dose-limiting OAR.

		VMAT	3D-CRT	IMRT	CYBER	TOMO	DSPT	IMPT
CTV	$D_{0.03\text{cc}}$	46.6	55.9	44.4*	45.3	42.7*	55.2	47.2
	D_{mean}	43.3	48.8	41.4	39.7	41.6	50.5	44.0
	$D_{99\%}$	41.6	35.6	39.7	35.1*	40.5	41.4	41.9*
PTV	$D_{0.03\text{cc}}$	47.6	55.9	44.9*	45.4	43.5*	55.5	47.3
	D_{mean}	43.3	48.0	41.1	38.7	41.9	49.4	43.4*
	$D_{99\%}$	40.2	33.9*	36.7	31.5**	40.2	38.8	39.5
Spinal cord	$D_{0.03\text{cc}}$	15.2	14.0	15.3	8.8*	15.0	13.0	8.5*
Oesophagus	$D_{0.03\text{cc}}$	27.7	24.3	24.4	21.6*	22.7	14.5	25.3
	D_{mean}	5.5	4.4	6.3	6.1	4.8	3.1*	4.8
Mediastinal envelope	$D_{0.03\text{cc}}$	39.6	42.2	36.3	35.0	38.0	44.8	42.4
Trachea	D_{mean}	5.3	4.9	5.4	6.6	5.5	2.5	4.0
	$D_{0.03\text{cc}}$	19.8	19.2	23.9	16.5	18.9	13.5	16.4
Left bronchus	D_{mean}	9.2	9.6	14.0	9.8	8.5	7.9	8.7
	$D_{2\%}$	16.6	20.9	22.1	12.3	16.2	16.2	25.0
Right bronchus	D_{mean}	8.9	8.7	9.4	7.5	9.7	3.5	8.2
	$D_{2\%}$	12.6	11.1	13.3	12.2	14.1	9.5	13.4
Lungs	D_{mean}	4.1	5.1	4.5	4.0	4.1*	3.4*	3.1*
	$V_{20\text{Gy}}$	5.0	8.6*	6.5*	3.7*	5.6	6.2	5.7
	$V_{5\text{Gy}}$	20.2	25.1	26.2	25.8	25.2*	13.5*	11.6**
Heart	D_{mean}	1.9	2.3	2.2	1.9	2.4**	0.2**	0.3**
	$V_{20\text{Gy}}$	0	0.1*	0*	0	0.9*	0	0
	$V_{5\text{Gy}}$	6.9	10.5	10.9	10.6	8.6*	0.7	1.8*
Integral body	D_{mean}	2.3	2.6*	2.5*	2.4*	2.5**	2.3	1.5*

CTV, clinical target volume; PTV, planning target volume; $D_{0.03\text{cc}}$ minimum dose to the 'hottest' 0.03 cc; D_{mean} mean dose to structure; $D_{2\%}$ highest dose to 2% of the volume; $D_{99\%}$ lowest dose to 99% of the volume; V_{xxGy} volume of a given structure receiving a radiation dose of xxGy. Outcomes are reported in Gy (dose) or percentage (volume).

* represents $p \leq 0.05$, ** $p \leq 0.001$, when compared to VMAT, respectively.

(Table 3). By doing so, the dose to both the CTV and PTV was revealed to not differ significantly from that of VMAT for any of the techniques. Nonetheless, it can be appreciated that both 3D-CRT and PSPT strictly kept to the OAR dose constraints and remained almost unchanged, whereas re-scaling indeed lead to down-scaling in CyberKnife and TomoTherapy plans. For all except for PSPT, the integral body dose statistically significantly differed from that delivered by VMAT. Most radiation doses to the assessed OARs were non-significantly different for the techniques used. Of note, the radiation dose to the heart and lungs was significantly reduced when using TomoTherapy, PSPT, or IMPT, whereby this was most pronounced in the D_{mean} and $V_{5\text{Gy}}$ respectively.

DISCUSSION

In the setting of a re-irradiation and in line with previous publications in the context of ROCOCO, the highly precise and conformal proton beam technique, IMPT, results in an equally good target coverage as VMAT, whilst reducing the dose to the OARs^{8,11}. This is, to our knowledge, the first *in silico* planning study addressing this particular topic of re-irradiation for (N)SCLC.

After having undergone high-dose radio(chemo)therapy with high doses to the OARs, therapeutic options in case of isolated local or (loco)regional disease are few. High-dose re-irradiation is hazardous and may lead to irreversible, potentially life-threatening complications. The review by De Ruyscher *et al.*² presented the studies or retrospective analyses performed and the potential detrimental effects. With more conformal radiation techniques, the occurrence of these side-effects may be reduced, however, not eliminated¹².

In the first multicentre phase II clinical study on re-irradiation with DSPT and IMPT, six of 57 patients developed a fatal complication, possibly (N=3) or probably (N=3) associated with high-dose re-irradiation to centrally located critical structures and concurrent chemotherapy. The median interval between initial irradiation and re-irradiation was 19 months (range 3.5-151 months), the median re-irradiation prescription dose was 66.6 Gy (30-74 Gy), and 68% of patients received concurrent chemotherapy. In total, 42% of the patients developed grade 3 or higher acute and/or late toxicities¹³. In-depth analysis revealed that overlap with the central airway region and doses to the heart and oesophagus were significantly associated with grade ≥ 3 toxicities. Most patients were treated with DSPT (60%) and there was no comparison with patients treated with IMPT. In a published retrospective series on 27 patients with re-irradiated thoracic cancers (excluding breast cancer) using IMPT, the risk of serious toxicity was notably lower¹⁴.

With a median re-irradiation dose of 66 Gy (range 42.3–84Gy) and despite 81% of the tumours being localised centrally (defined as tumour ≤ 2 cm of any critical mediastinal structures), only 7% of the patients experienced grade 3 pulmonary toxicity and no grade 4 or 5 toxicities occurred. In a more recent prospective multicentre registry analysis of 79 patients with lung cancer who underwent proton re-irradiation, toxicity overall was lower, with acute and late grade 3 toxicities occurring in 6% and 1%, respectively, and three patients dying after re-irradiation from possible radiation-induced toxicity ¹⁵.

Other therapeutic options are also being explored. These included targeted agents tailored to the tumour's molecular profile ¹⁶⁻¹⁸. Moreover, immunotherapy is increasingly being used in the palliative setting, but also in the context of locally recurrent disease. Peters *et al.* ¹⁹ summarized the use of programmed death 1 (PD-) blockade in advanced, *i.e.*, recurrent or metastatic, NSCLC patients. In particular pembrolizumab, a monoclonal antibody directed at PD-1, has demonstrated survival benefits in several studies across solid tumours, including in NSCLC. Taking it one step further, immunotherapy combined with palliative as well as high-dose re-irradiation (in adjuvant setting) is a therapeutic option currently being explored ²⁰. Even though these rather novel approaches are promising and may improve clinical outcomes, also they may harbour side-effects: in the case of immunotherapy, patients may develop pneumonitis. Therefore, those patients having been treated with high-dose thoracic radio(chemo)therapy need to be monitored with particular caution ²¹.

From this plethora of tailored therapeutic options and individual patients' tumour biology, it becomes clear that clinical randomised studies with fixed doses to the target and a set systemic treatment are not likely to be feasible. Instead, treatment needs to be aligned to the molecular profile of the tumour and to the remaining tolerance doses to OARs. With deformable image and dose registration algorithms, the dose from the first radiation course can be deformed to the re-irradiation planning CT, to guide dose planning and evaluation ^{14,22}. Additionally, factors such as the interval between initial treatment and time to recurrent disease, use of concurrent systemic therapy, as well as the experience of the treating department need to be taken into account.

This ROCOCO study holds some limitations. First, the participating centres performed the treatment planning according to a strict, previously consented, protocol. Despite this, experience of the treatment planner may have differed and thus results in varying outcomes. Second, even though the study was based on 4D-PET-CT data, only the mid-ventilation data were used in this study and thus no internal target volume deployed. This approach was chosen since the different radiation techniques require different strategies to take tumour and anatomical motion into account. This is caused by their

different sensitivity to changes in tissue density in the beam path and the accompanying variation in beam bath, *i.e.*, the interplay effect. Different strategies to overcome this hurdle are being explored, but these are beyond the scope of this treatment planning study^{6,23,24}. Third, even though it is not uniformly clinical practice in proton beam irradiation, treatment plans were calculated using a given PTV without considering additional uncertainty margins. Results for target coverage were nonetheless given for both CTV and PTV. Fourth, in the absence of normal tissue complication models for proton beams, the ones established for photons were considered in calculating the remaining tolerance dose to the OARs⁷. Most importantly, these data need to be gathered and will indeed be collected within the model-based approach²⁵.

CONCLUSION

In conclusion, highly conformal photon and proton beam techniques enable high-dose re-irradiation of the target volume. They, however, significantly differ in the dose deposited in the OARs. The therapeutic options, *i.e.*, re-irradiation or systemic therapy, need to be carefully weighed and discussed with patients.

Supplementary Table: The individual dose constraints (given in Gy) for the patients included in this in silico study

	PATIENT																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Lungs (D_{mean})	10,3	17,6	12,6	3,6	7,9	4,1	13,1	7,6	3,4	6,1	10,5	3,3	9,2	7,4	9,0	5,8	3,6	2,3	5,6	11,1	9,8	9,2	12,2	13,9
PRV mediastinum (D_{max})	46,8	37,2	70	46,1	46,2	51,1	66,6	62,1	50,8	37,1	63,1	36,2	44,9	60,3	47,7	37,2	39,8	37,3	70	41,1	59,4	51,4	46,3	70
Oesophagus (D_{max})	37,7	26,2	65	37,5	65	41,2	65	51,6	41,4	40,6	62,8	43	49	53,4	37,9	33,7	30,6	31,4	29,3	33,6	65	44	52,2	65
Trachea (D_{max})	45,3	37,1	70	48	70	50,4	70	61,3	52,8	40,2	64,4	59	42,3	61	50,4	42,2	41,9	38,4	39,8	43,8	70	51,4	70	70
Brachial plexus (D_{max})	32,6	17,7			58,8			38,8			53,3			38,6					20,2 (IL)/ 60,0 (CL)		26,4		60	
Spinal cord (D_{max})	41,2	41,1	19,6	25,3	45	37,4	45	22,9	34,6	27,2	42,9	45	24,2	33,6	36,8	24,6	20,6	36	14,7	42	39,9	14,3	39,8	45
Heart (D_{mean})	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46	46
Ribs (D_{max})	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35	35
Chest wall (D_{max})	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40

REFERENCES

1. van Baardwijk A, Wanders S, Boersma L, 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):1380-1386.
2. De Ruyscher D, Faivre-Finn C, Le Pechoux C, Peeters S, Belderbos J. High-dose re-irradiation following radical radiotherapy for non-small-cell lung cancer. *Lancet Oncol*. 2014;15(13):e620-624.
3. Vyfhuis MAL, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *J Thorac Dis*. 2018;10(Suppl 21):S2522-S2536.
4. Chang JY, Verma V, Li M, et al. Proton Beam Radiotherapy and Concurrent Chemotherapy for Unresectable Stage III Non-Small Cell Lung Cancer. Final Results of a Phase 2 Study. *JAMA Oncol*. 2017;3(8):e172032.
5. Wink KC, Roelofs E, Solberg T, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol*. 2014;4:292.
6. Jakobi A, Perrin R, Knopf A, Richter C. Feasibility of proton pencil beam scanning treatment of free-breathing lung cancer patients. *Acta Oncol*. 2018;57(2):203-210.
7. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S70-76.
8. Roelofs E, Engelsman M, Rasch C, et al. Results of a multicentric in silico clinical trial (ROCOCO): comparing radiotherapy with photons and protons for non-small cell lung cancer. *J Thorac Oncol*. 2012;7(1):165-176.
9. Eekers DBP, Roelofs E, Cubillos-Mesias M, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric in silico ROCOCO trial. *Acta Oncol*. 2019;58(1):57-65.
10. Eekers DBP, Roelofs E, Jelen U, et al. Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric in silico ROCOCO trial. *Radiother Oncol*. 2016;121(3):387-394.
11. Wink KCJ, Roelofs E, Simone CB, 2nd, et al. Photons, protons or carbon ions for stage I non-small cell lung cancer - results of the multicentric ROCOCO in silico study. *Radiother Oncol*. 2018;128(1):139-146.
12. Verma V, Rwigema JM, Malyapa RS, Regine WF, Simone CB, 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. *Radiother Oncol*. 2017;125(1):21-30.
13. Chao HH, Berman AT, Simone CB, 2nd, et al. Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017;12(2):281-292.
14. Ho JC, Nguyen QN, Li H, et al. Reirradiation of thoracic cancers with intensity modulated proton therapy. *Pract Radiat Oncol*. 2018;8(1):58-65.
15. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical Outcomes of Patients With Recurrent Lung Cancer Reirradiated With Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies. *Pract Radiat Oncol*. 2019;9(4):280-288.
16. Sabari JK, Santini F, Bergagnini I, Lai WV, Arbour KC, Drilon A. Changing the Therapeutic Landscape in Non-small Cell Lung Cancers: the Evolution of Comprehensive Molecular Profiling Improves Access to Therapy. *Curr Oncol Rep*. 2017;19(4):24.
17. Rooney C, Sethi T. Advances in molecular biology of lung disease: aiming for precision therapy in non-small cell lung cancer. *Chest*. 2015;148(4):1063-1072.

18. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell*. 2015;160(1-2):48-61.
19. Peters S, Kerr KM, Stahel R. PD-1 blockade in advanced NSCLC: A focus on pembrolizumab. *Cancer Treat Rev*. 2018;62:39-49.
20. Evans T, Ciunci C, Hertan L, Gomez D. Special topics in immunotherapy and radiation therapy: reirradiation and palliation. *Transl Lung Cancer Res*. 2017;6(2):119-130.
21. Manapov F, Roengvoraphoj O, Dantes M, Marschner S, Li M, Eze C. Pneumonitis in Irradiated Lungs After Nivolumab: A Brief Communication and Review of the Literature. *J Immunother*. 2018;41(2):96-99.
22. Boman E, Kapanen M, Pickup L, Lahtela SL. Importance of deformable image registration and biological dose summation in planning of radiotherapy retreatments. *Med Dosim*. 2017;42(4):296-303.
23. Boda-Heggemann J, Knopf AC, Simeonova-Chergou A, et al. Deep Inspiration Breath Hold-Based Radiation Therapy: A Clinical Review. *Int J Radiat Oncol Biol Phys*. 2016;94(3):478-492.
24. Bernatowicz K, Lomax AJ, Knopf A. Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients. *Phys Med Biol*. 2013;58(22):7905-7920.
25. Langendijk JA, Lambin P, De Ruyscher 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):267-273.

CHAPTER 8

General discussion and future perspectives

GENERAL DISCUSSION

The main purpose of this thesis was to investigate innovative strategies to optimize the treatment and thus outcome of non-small cell lung cancer (NSCLC), without increasing treatment toxicity. With regard to this main purpose, the following topics were addressed:

- Lymph node recurrence following SABR for early stage NSCLC
- Metformin use during concurrent chemoradiotherapy for locally advanced NSCLC
- Particle therapy for early stage and recurrent NSCLC

In this general discussion, I will go back to the original hypotheses on each of these topics and discuss the main findings in view of the currently available evidence. Future perspectives on how to (further) improve the outcome for patients with NSCLC are also provided.

LYMPH NODE RECURRENCE FOLLOWING SABR FOR EARLY STAGE NSCLC

In **chapter 2**, the results of a systematic review on the outcome of SABR with respect to the regional lymph nodes are described. The literature was searched for information on the incidence of and risk factors for regional recurrence (RR) following SABR and surgery for early stage NSCLC ¹. We included sixteen studies, mostly retrospective, and found a mean incidence of RR of almost 10%. This rate was similar in the surgical studies we included, despite the intra-operative systemic mediastinal lymphadenectomy. For the risk of RR following SABR, (incidental) hilar and/or mediastinal dose seemed to be relevant and males and anaemic patients were reported to be at higher risk for nodal failure. Occult nodal involvement, visceral pleural invasion (VPI) and lymphovascular space invasion (LVI) were risk factors in most surgical studies. These pathological risk factors cannot be tested for prognostic value in patients treated with SABR, due to the lack of resected tissue. However, we were intrigued by the possibility to quantify the presence and type of pleural contact on the CT used for SABR planning as a surrogate for VPI ².

We hypothesised that visceral pleural invasion (VPI) was also risk factor for (isolated) regional recurrence following SABR. To this end, we performed a retrospective cohort study on 554 patients treated with SABR in one of three radiation oncology departments (MAASTRO clinic, Netherlands Cancer Institute in the Netherlands, or the University Hospital Carl Gustav Carus of the Technische Universität Dresden in Germany).

Chapter 3 describes the results of this study on the potential correlation of the extent of pleural contact with isolated regional recurrence in 494 patients. In the investigated cohort, the most common type of recurrence was distant (almost 20%). IRR occurred in 21 patients (4%), of whom 9 (43%) received best supportive care. Only 7 patients (33%) received radical treatment³. This number of radically treated patients is quite low and indicative of the type of patients treated within our study: elderly patients (median age 74 years) and probably unfit for surgery due to their age and/or comorbid disease. Surgery was (and still is) the mainstay of treatment for early stage NSCLC, but elderly patients undergo surgery less often⁴.

Contact of the tumour with the pleura did not prove to be a relevant factor in terms of regional and distant control. This is contrary to results obtained in surgical studies, where the prognostic value of VPI was confirmed in multiple clinical trials^{5,6}. None of the other factors were related to isolated regional recurrence. The cT-stage significantly correlated with the occurrence of distant metastases.

Since the publication of our study, others have attempted to identify factors associated with nodal or distant recurrence^{7,8}. A retrospective study on 363 patients with early stage NSCLC treated with SABR found GTV and prescribed dose to be associated with time to (nodal or distant) metastasis⁷. Miller *et al.*⁸ only found patient age to be relevant (younger patients had a higher risk of developing metastasis) in 292 patients treated with SABR, the remaining clinical factors that were tested were not predictive. Failure rates in both these studies were comparable to the rates in our study. None of the aforementioned studies investigated the prognostic value of pleural contact, which is a unique feature of our study. Pleural contact is the only imaging feature we evaluated. In hindsight, another aspect that would have been interesting to include in our study is the presence of fissure attachment. In our study, we did not differ between VPI of the thoracic pleura or the interlobar fissure. However, Liu *et al.*⁹ discovered that attachment of the tumour to the fissure and not the pleura was associated with pathologic lymph node involvement on surgical lymph node dissection. In future studies, more imaging features from the pre-SABR planning CT should be analysed and linked to patient outcome. This is a contemporary field of research termed 'radiomics'. Encouraging results have been published, with radiomic features predicting disease free survival, overall survival, freedom from nodal failure following SABR or pathological nodal involvement in surgically treated patients⁹⁻¹¹.

Another route towards an individualised treatment may be the use of cancer genomics and molecular profiling. Through histo-molecular classification of the primary tumour, high risk features can be identified from tumour tissue and/or patient blood samples.

This field of research is evolving rapidly, with for example the potential use of circulating tumour DNA to non-invasively genotype the cancer and/or detect residual disease following treatment¹²⁻¹⁴. Molecular testing on for example epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), v-Ki-ras 2 Kirsten rat sarcoma viral oncogene homolog (KRAS) status or programmed death-ligand 1 (PDL-1) expression may help select the appropriate adjuvant targeted or immunotherapy^{8,15}.

METFORMIN FOR THE TREATMENT OF LUNG CANCER

We hypothesised that the use of metformin during concurrent chemoradiotherapy could improve outcome for patients with locally advanced NSCLC treated with concurrent chemoradiotherapy. To test our hypothesis, we performed a multi-institutional retrospective cohort study on 682 patients treated with concurrent chemoradiotherapy between 2008 and 2013, of which 59 patients had used metformin during their lung cancer treatment. The results are described in **chapter 4**. Interestingly, fewer distant metastases occurred in patients using metformin compared with the control group (74% versus 53% at 2 years; $p=0.01$) and progression free survival also improved (58% versus 37% at 2 years; $p=0.01$)¹⁶. Naturally, as stated in the discussion section of the manuscript, the retrospective nature of our study has led to several important limitations. Therefore, our results should be interpreted with caution.

Metformin is very attractive to repurpose for the treatment of non-small cell lung cancer or other cancer types. It costs only a fraction of standard chemotherapeutic agents, targeted, or immunotherapies, generally has few side effects and can be taken at home. Based on encouraging results from pre-clinical and observational studies, there is a potential clinical benefit of metformin in several settings. Anti-cancer effects have been described for metformin as a single agent or combined with other anti-cancer agents such as ionising radiation, chemotherapy, targeted and immunotherapy¹⁷. Several research groups have started prospective clinical studies on the effect of metformin (with or without chemo- and/or radiotherapy) in patients with lung cancer or other types of cancer¹⁷⁻¹⁹. Currently, 310 clinical studies are investigating metformin in cancer in general (www.clinicaltrials.gov, January 2019). Of these, twelve studies focus on non-small cell lung cancer. Unfortunately, several trials had to close early due to slow accrual (NCT01578551, NCT01997775, NCT02285855, NCT02019979), two of which have published their results^{20,21}. In a not fully accrued single arm phase II trial, Parikh *et al.*²⁰ evaluated the combination of standard chemotherapy with metformin in fourteen patients with advanced NSCLC. Limited by the small sample size, the authors concluded combining metformin with chemotherapy was safe as toxicity was mild. Clinical outcome

did not seem to be improved compared to other phase III studies in advanced NSCLC. Another twenty-five patients with metastatic non-squamous NSCLC were enrolled in a randomised phase II study comparing two arms with standard platinum based chemotherapy and Bevacizumab, with or without metformin ²¹. Progression-free survival was longer for those patients receiving metformin (median 9.6 months *versus* 6.7 months, $p=0.024$), without a significant difference in overall survival. Several other studies are still recruiting patients or have been completed and are awaiting results, mainly in stage IV patients, combining metformin with standard chemotherapy and/or targeted therapy or immunotherapy.

Currently, there are two active randomised clinical trials in stage III patients, the patient category investigated in the current thesis. Actual enrolment for both studies is unknown and both estimated study completion dates are within the next 3 years. Estimated enrolment numbers are substantial: 168 patients (NCT02186847) and 94 patients (NCT02115464). If successful, these studies might show us whether the anti-cancer effects observed in preclinical studies will translate into an improved disease outcome for the locally advanced NSCLC patient population.

Another important aspect in this patient category is toxicity. While the (limited) prospective data on metformin use during systemic therapy do not show an increased risk of adverse events in the metastatic NSCLC population, the question whether metformin use during concurrent chemoradiotherapy will increase healthy tissue radiation sensitivity and thus potentially increase radiation toxicity still needs to be answered. Unfortunately, in our retrospective analysis we were not able to evaluate toxicity as adverse events were not systematically scored or not available for the patients included in our study.

Elderly patients may also be very suitable for adjuvant or concurrent treatment with metformin in the palliative or curative setting. It has been shown that elderly patients >70 years are less likely to receive any (curative) treatment and less often receive concurrent chemotherapy ^{22,23}. If comorbidities and age make stage III elderly patients unfit for concurrent or sequential chemotherapy, perhaps metformin can be added to radical radiotherapy, ideally without increasing radiation toxicity.

PARTICLE THERAPY

Early stage NSCLC

We hypothesised that stereotactic particle radiotherapy could significantly reduce the dose to organs at risk and thus lower the risk of treatment toxicity and enable isotoxic dose escalation in early stage NSCLC patients. We performed a multicentric planning study together with partners of the Radiation Oncology Collaborative Comparison (ROCOCO) consortium²⁴. The results are outlined in **chapter 6**. The dose to the organs at risk (OARs) was compared and dose-escalation possibilities were explored in 24 cases of early stage NSCLC, for five modalities: intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), CyberKnife, double scattered proton therapy (DSP) and an intensity-modulated carbon-ion therapy (IMIT). Our study showed that in general, particle therapy (especially IMIT) results in the highest relative dose reduction to most OARs compared to IMRT, as was expected. However, the dosimetric advantage of particles is probably too modest to be clinically relevant for most patients in the early stage NSCLC setting. On top of that, several clinical studies on photon SABR for early stage NSCLC patients report high rates of local control and a good tolerability, even in patients with severe comorbidity and/or poor pulmonary function²⁵⁻²⁸. Therefore, it is likely that the typical SABR patient with a small, peripheral lesion will not significantly benefit from proton or carbon-ion SABR. The results of our planning study confirm this statement and show these patients are probably best off with VMAT or Cyberknife and not with particle therapy. The consensus statement of the International Particle Therapy Cooperative Group (PTCOG) that was published in 2016 also states that there is no clear role for proton therapy in small, peripheral pulmonary tumours²⁹. Our results serve as a proof of concept that particle therapy is of little benefit in small peripheral tumours.

Our study showed that DSP with a two or three beam set up (3-dimensional (3D) conformal treatment planning) performed worst for several OARs and was often the limiting factor for dose escalation. We did not compare DSP with the more advanced pencil beam scanning (PBS) technique. Most proton centres that are currently being built around the world will use PBS, because passive scattering proton therapy (PSPT) lacks the possibility of intensity modulation³⁰. The first clinical results of PBS for early stage NSCLC have been published and report high local control rates and low toxicity³¹. However, it is likely that PBS plans would have been similar to our IMIT plans and would not have changes our conclusions with respect to the small peripheral lesions. Though more conformal, PBS for thoracic tumours is more challenging than PSPT and IMRT, because intra- and interfractional changes (e.g. size of the breathing motion and its interplay with the motion of the beam, tissue density changes, organ motion, anatomic changes) influence the proton range and thus the dose distribution^{30,32}.

Future research and treatment experience is needed to determine which patients with NSCLC will benefit from particle therapy. Three proton therapy centres are currently treating patients in the Netherlands and are located in Delft, Groningen and Maastricht. All centres use PBS and have not yet started treating patients with lung cancer, due to the challenges with respect to breathing motion and other factors influencing the proton range, as was mentioned earlier. To select patients for proton therapy, several tumour specific committees are formulating national indication protocols per tumour type using the model based approach³³. This approach is based on normal tissue complication probability (NTCP) models, aiming to select those patients who will experience significantly fewer serious adverse events when treated with proton therapy instead of X-rays^{34,35}. The selected NTCP models will continuously be prospectively validated and adjusted if needed, using the data of an enlarging group of patients treated with proton therapy. This method of prospectively validating and repeatedly adjusting NTCP models by including patients in a data registration program is termed the rapid learning method^{33,35}. It is unlikely that small peripheral lung tumours will achieve the required difference in complication probability, as the baseline risk of serious toxicity is already low. Perhaps a benefit can exist in select cases of early stage NSCLC where photon SABR is difficult or contraindicated. Examples include a central tumour location, a re-irradiation setting, large tumours (>4cm), apical tumours close to the brachial plexus or multiple primary tumours^{36,37}.

Another patient category potentially able to benefit from the OAR dose reductions achieved by particle therapy is the patient with interstitial lung disease (ILD). ILD is characterised by diffuse, inflammatory or fibrotic changes of the lung parenchyma, often resulting in a mainly restrictive defect on pulmonary function testing³⁸. Idiopathic pulmonary fibrosis (IPF) is the most serious form of ILD³⁹. IPF patients have an up to seven times higher risk of developing lung cancer³⁹. Treatment of lung cancer in ILD patients is a challenge, due to increased morbidity and mortality risks associated with each type of treatment. In a systematic review, a weighted proportion of SABR related mortality of 15.6% and ILD-specific toxicity of 25% was reported. The SABR-related mortality rate increased to 33% for studies on only IPF patients and treatment related toxicity to 71%. In a subgroup analysis, less treatment-related mortality and toxicity occurred when a smaller volume of the lung received 20Gy (V20Gy) and the mean lung dose (MLD) was lower³⁸. As these parameters are probably lower when using particle therapy (as was the case in our planning study in the IMIT plans), there is a rationale for the use of particle therapy in ILD patients. Even a small difference in dose to the surrounding lung may be relevant in these patients. In a recent retrospective study on 30 IPF patients with stage I-II NSCLC treated with either X-ray (22 patients) or proton irradiation (8 patients), 18% of the patients treated with X-rays died of treatment related pulmonary toxicity

and none of the patients treated with protons. The authors also report a trend for an improved 1-year overall survival for those treated with proton therapy⁴⁰. However, in the systematic review described earlier, particle beam therapy related mortality and toxicity were still high (4.3% and 18.2%)³⁸. This highlights the need for prospective trials on intensity modulated particle beam therapy in patients with lung cancer and coexisting ILD, incorporating and differentiating in the type and severity of the ILD.

Recurrent NSCLC

We hypothesised that proton therapy for recurrent NSCLC could significantly decrease the dose to surrounding (previously irradiated) healthy tissues, enabling re-irradiation to a higher dose than what would be possible with photon therapy. We performed a multicentric planning study within the ROCOCO consortium for 24 NSCLC patients treated with re-irradiation. Each patient case had individual dose constraints for the OARs based on the previous irradiation. The results of are outlined in **chapter 7**. The dose to the OARs and planning target volume (PTV) coverage were compared for seven modalities: VMAT, three-dimensional conformal radiation therapy (3D-CRT), IMRT, Tomotherapy, CyberKnife, DSP and IMPT. The two modalities lacking intensity modulation, 3D-CRT and DSP, could not reach as much PTV coverage as the other modalities. The main conclusion of our study is that with a similar PTV coverage, the IMPT plans resulted in a lower mean dose to the heart and lungs and a smaller volume of the lung receiving 5Gy compared to VMAT. Mean and (near) maximum doses to other organs at risk (e.g. oesophagus, bronchi and mediastinal structures) were comparable or slightly better with IMPT.

Meanwhile, the first prospective clinical results of re-irradiated non-small cell lung cancers have been published⁴¹⁻⁴³. Passive scatter proton therapy was the predominant form of proton beam delivery in most series. While the clinical outcomes with respect to locoregional control and OS were acceptable, the incidence and degree toxicities varied considerably. In one of the studies, as many as 6/57 patients (10%) experienced grade 5 toxicities and 24 patients (42%) had $\geq$ acute or late grade 3 toxicities⁴². Ho *et al.*⁴⁴ have published a retrospective analysis of 27 patients re-irradiated with IMPT for recurrent thoracic malignancies (81% had NSCLC). In this study, only 2 patients (7%) developed late grade 3 pulmonary toxicity and no grade 4 or 5 toxicities occurred. The difference in toxicity between the studies is likely the result of variation in for example the technique used (DSP or IMPT), chemotherapy usage, re-irradiation interval, tumour volume, central tumour location (within 2 cm of the bronchial tree) and experience with treatment planning and delivery⁴¹. Therefore, patient selection is very important when considering (proton) re-irradiation and caution is required. As presented in our planning study, doses to OAR are often lower with IMPT. However, with a PTV close to or overlapping previously irradiated critical structures, serious toxicity remains a concern

with re-irradiation, also with protons. Prospective data on re-irradiation with IMPT are necessary. Factors predisposing towards higher toxicity need to be identified to isolate those patients that are the most likely to benefit ⁴¹.

FUTURE PERSPECTIVES

In early stage NSCLC, further research is needed on the risk of and prognostic factors for recurrence following SABR, to guide clinicians and patients with respect to diagnostic, treatment and follow-up strategies. For example, patients at high risk for (occult) nodal metastases may benefit from more invasive mediastinal evaluation and patients at high risk for regional or distant recurrence may benefit from adjuvant systemic therapy (e.g. chemotherapy or immunotherapy) following SABR ^{15,45}. Favouring the concept of personalised medicine and from a cost-effective standpoint, it is important to select the appropriate diagnostic procedures and treatment for the right patient. To this end, patient selection tools are vital as the type of patient and type of tumour are heterogeneous. Especially in the SABR population, clinical, imaging and molecular factors need to be incorporated in prediction models as histological information is often absent or limited to biopsy material.

For patients with locally advanced NSCLC, only modest improvements in outcome have been reported over the last decade ⁴⁶. In a retrospective cohort study, we showed that metformin may be beneficial in this patient category as fewer distant metastases occurred and progression free survival was longer in patients using metformin during concurrent chemoradiotherapy. These results deserve further research in a prospective, randomised setting. Two active randomised clinical trials investigating metformin use in stage III NSCLC patients are on the way (www.clinicaltrials.gov, NCT02186847 and NCT02115464) and will hopefully provide more information on the effectiveness of metformin in NSCLC. The role of metformin in the era of immunotherapy should also be of interest. Recent research has shown that the use of Durvalumab (a programmed death ligand-1 (PD-L1) blocker) significantly improved in overall survival in the adjuvant setting in locally advanced NSCLC (66% *versus* 56% at 2 years) ⁴⁷. There is a rationale for the combination of metformin with immune checkpoint inhibitors to further improve outcome, as metformin reduces tumour hypoxia and thereby enhances the programmed cell death protein-1 (PD-1) blockade ^{48,49}. Metformin has also been shown to increase cytotoxic T lymphocyte activity by reducing tumour PD-L1 levels and thus decrease binding with PD-1 ⁵⁰.

The optimal clinical context for particle therapy for NSCLC remains to be defined. Although disease control is expected to be comparable to photon therapy, the clinical results from proton therapy (mainly PBS) for NSCLC need to be awaited. From the data registered in the prospective databases in rapid learning health care, the difference in toxicity and disease outcome can be measured. The majority of the registered data will most likely involve locally advanced patients with large treatment fields, as the dosimetric difference and thus gain in complication probability will be the largest in these patients. However, it remains important to perform planning and clinical studies in the early stage NSCLC patient, for example to explore the possibility of increased tumour control through isotoxic dose escalation. Furthermore, relevant indications for proton therapy can be present in case no NTCP models exist (e.g. for brachial plexus neuropathy) or when existing models are not applicable (e.g. in the re-irradiation or ILD setting).

For research on a new technology such as IMPT to be successful, collaboration is of vital importance. Not only between (inter)national radiotherapy centres, but also within hospitals and departments itself to gain enough support for the intended research and to cover all relevant aspects. Histologic, immunologic and radiobiologic data should form the basis and be linked to toxicity and clinical outcomes to gain solid evidence of efficacy. An example of a patient category to incorporate all of these aspects are patients with a superior sulcus tumour. Superior sulcus tumours (frequently termed as Pancoast tumours) are tumours located in the apex of the lung, with potential invasion of bones (ribs, vertebrae), subclavian vessels or the brachial nerve plexus⁵¹. The majority of superior sulcus tumours are non-small cell lung cancers. Treatment typically involves concurrent chemoradiotherapy up to 45-66 Gy (resectable tumours) or 60-66Gy (potentially resectable tumours), followed by a resection when feasible to achieve optimal local control⁵²⁻⁵⁵. Induction treatment with protons can provide a unique possibility to evaluate pathological complete response rates, characterise the local and systemic immunological response and assess radiobiological, molecular and vascular effects of protons in the tumour and/or 'healthy' lung tissue (e.g. DNA damage and gene expression). Furthermore, studies have shown that the volume of irradiated lung and dose volume parameters are associated with the risk of postoperative pulmonary complications after thoracic chemoradiotherapy^{56,57}. With protons, the irradiated lung volume and radiation dose to the lungs can be reduced, thereby potentially reducing the morbidity from subsequent surgery.

CONCLUSIONS

In the current thesis, several innovative strategies were evaluated aiming to improve the outcome for patients with potentially curable (stage I-III) NSCLC. To be able to improve disease outcome and avoid over- or undertreatment, it is important to select the right diagnostic tool and the appropriate treatment for each patient. To this end, prediction models incorporating relevant risk factors for recurrence are necessary to help physicians and patients make decisions. Patients with the highest risk of recurrence could benefit from more intensive diagnostic work-up and more aggressive treatment and follow-up regimens. We performed a systematic review and a retrospective study on early stage NSCLC patients treated with SABR in search of relevant risk factors for (isolated) regional recurrence (a potentially curable situation). We used the presence and type of pleural contact on pre-SABR planning CTs as a surrogate for visceral pleural invasion, a known risk factor for occult nodal metastases and regional recurrence in surgical studies. Pleural contact and several other variables did not show a correlation with (isolated) regional recurrence. Further research also incorporating imaging (radiomics) and molecular factors is warranted.

In locally advanced patients, the effect of metformin use during concurrent chemoradiotherapy was studied. An improved progression free and distant metastasis free survival was shown for the patients using metformin. These results merit confirmation in a randomised controlled trial and the added role of metformin in the era of immunotherapy needs to be defined.

We evaluated particle therapy for early stage and recurrent NSCLC in two *in silico* trials, performed within the ROCOCO consortium. In early stage NSCLC, it was shown that the typical SABR patient with a small, peripheral lesion will probably not benefit from proton or carbon-ion SABR. Furthermore, in both planning studies limitations in plans using DSP were evident. In the early stage setting, dose escalation probabilities were worst with DSP (mainly due the beam arrangements) and in the re-irradiation setting the lack of intensity modulation compromised PTV coverage.

REFERENCES

1. Wink KCJ, van Baardwijk A, Troost EGC, De Ruyscher D. Nodal recurrence after stereotactic body radiotherapy for early stage non-small cell lung cancer: Incidence and proposed risk factors. *Cancer Treat Rev.* 2017;56:8-15.
2. Imai K, Minamiya Y, Ishiyama K, et al. Use of CT to evaluate pleural invasion in non-small cell lung cancer: measurement of the ratio of the interface between tumor and neighboring structures to maximum tumor diameter. *Radiology.* 2013;267(2):619-626.
3. Wink KCJ, Löck S, Rossi M, et al. Contact of a tumour with the pleura is not associated with regional recurrence following stereotactic ablative radiotherapy for early stage non-small cell lung cancer. *Radiotherapy and Oncology.* 2019;131:120-126.
4. Driessen E, Detillon D, Bootsma G, et al. Population-based patterns of treatment and survival for patients with stage I and II non-small cell lung cancer aged 65-74years and 75years or older. *J Geriatr Oncol.* 2019.
5. Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion is an invasive and aggressive indicator of non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2005;130(1):160-165.
6. Jiang L, Liang W, Shen J, et al. The impact of visceral pleural invasion in node-negative non-small cell lung cancer: a systematic review and meta-analysis. *Chest.* 2015;148(4):903-911.
7. Cerra-Franco A, Liu S, Azar M, et al. Predictors of Nodal and Metastatic Failure in Early Stage Non-small-cell Lung Cancer After Stereotactic Body Radiation Therapy. *Clin Lung Cancer.* 2018.
8. Miller CJ, Martin B, Stang K, et al. Predictors of Distant Failure After Stereotactic Body Radiation Therapy for Stages I to IIA Non-Small-Cell Lung Cancer. *Clin Lung Cancer.* 2019;20(1):37-42.
9. Liu Y, Kim J, Balagurunathan Y, et al. Prediction of pathological nodal involvement by CT-based Radiomic features of the primary tumor in patients with clinically node-negative peripheral lung adenocarcinomas. *Medical physics.* 2018;45(6):2518-2526.
10. Li H, Galperin-Aizenberg M, Pryma D, Simone CB, 2nd, Fan Y. Unsupervised machine learning of radiomic features for predicting treatment response and overall survival of early stage non-small cell lung cancer patients treated with stereotactic body radiation therapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology.* 2018;129(2):218-226.
11. Bousabarah K, Temming S, Hoevels M, et al. Radiomic analysis of planning computed tomograms for predicting radiation-induced lung injury and outcome in lung cancer patients treated with robotic stereotactic body radiation therapy. *Strahlenther Onkol.* 2019.
12. Comino-Mendez I, Turner N. Predicting Relapse with Circulating Tumor DNA Analysis in Lung Cancer. *Cancer Discov.* 2017;7(12):1368-1370.
13. Chaudhuri AA, Chabon JJ, Lovejoy AF, et al. Early Detection of Molecular Residual Disease in Localized Lung Cancer by Circulating Tumor DNA Profiling. *Cancer Discov.* 2017;7(12):1394-1403.
14. Yeung KT, More S, Woodward B, Velculescu V, Husain H. Circulating Tumor DNA for Mutation Detection and Identification of Mechanisms of Resistance in Non-Small Cell Lung Cancer. *Mol Diagn Ther.* 2017;21(4):375-384.
15. Sebastian NT, Xu-Welliver M, Williams TM. Stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC): contemporary insights and advances. *J Thorac Dis.* 2018;10(Suppl 21):S2451-S2464.
16. Wink KC, Belderbos JS, Dieleman EM, et al. Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during

- concurrent chemoradiotherapy. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2016;118(3):453-459.
17. Levy A, Doyen J. Metformin for non-small cell lung cancer patients: Opportunities and pitfalls. *Critical reviews in oncology/hematology*. 2018;125:41-47.
 18. Troncone M, Cargnelli SM, Villani LA, et al. Targeting metabolism and AMP-activated kinase with metformin to sensitize non-small cell lung cancer (NSCLC) to cytotoxic therapy: translational biology and rationale for current clinical trials. *Oncotarget*. 2017;8(34):57733-57754.
 19. Chae YK, Arya A, Malecek MK, et al. Repurposing metformin for cancer treatment: current clinical studies. *Oncotarget*. 2016;7(26):40767-40780.
 20. Parikh AB, Kozuch P, Rohs N, Becker DJ, Levy BP. Metformin as a repurposed therapy in advanced non-small cell lung cancer (NSCLC): results of a phase II trial. *Investigational new drugs*. 2017;35(6):813-819.
 21. Marrone KA, Zhou X, Forde PM, et al. A Randomized Phase II Study of Metformin plus Paclitaxel/Carboplatin/Bevacizumab in Patients with Chemotherapy-Naive Advanced or Metastatic Non-squamous Non-Small Cell Lung Cancer. *The oncologist*. 2018;23(7):859-865.
 22. Miller ED, Fisher JL, Haglund KE, et al. Identifying patterns of care for elderly patients with non-surgically treated stage III non-small cell lung cancer: an analysis of the national cancer database. *Radiation oncology*. 2018;13(1):196.
 23. Driessen EJM, Schulkes KJG, Dingemans AC, et al. Patterns of treatment and survival among older patients with stage III non-small cell lung cancer. *Lung Cancer*. 2018;116:55-61.
 24. Wink KCJ, Roelofs E, Simone CB, 2nd, et al. Photons, protons or carbon ions for stage I non-small cell lung cancer - Results of the multicentric ROCOCO in silico study. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2018;128(1):139-146.
 25. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303(11):1070-1076.
 26. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *International journal of radiation oncology, biology, physics*. 2014;88(5):1092-1099.
 27. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol*. 2015;16(6):630-637.
 28. Timmerman RD, Hu C, Michalski JM, et al. Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer. *JAMA Oncol*. 2018;4(9):1287-1288.
 29. Chang JY, Jabbour SK, De Ruyscher D, et al. Consensus Statement on Proton Therapy in Early-Stage and Locally Advanced Non-Small Cell Lung Cancer. *International journal of radiation oncology, biology, physics*. 2016;95(1):505-516.
 30. Chang JY, Zhang X, Knopf A, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. *International journal of radiation oncology, biology, physics*. 2017;99(1):41-50.
 31. Chen J, Lu JJ, Ma N, et al. Early stage non-small cell lung cancer treated with pencil beam scanning particle therapy: retrospective analysis of early results on safety and efficacy. *Radiation oncology*. 2019;14(1):16.
 32. Wink KC, Roelofs E, Solberg T, et al. Particle therapy for non-small cell lung tumors: where do we stand? A systematic review of the literature. *Front Oncol*. 2014;4:292.

33. Boersma LJ, van Vulpen M, Rasch CRN, Langendijk JLA. [Proton therapy centres opened; what next?]. *Nederlands tijdschrift voor geneeskunde*. 2018;162.
34. Widder J, van der Schaaf A, Lambin P, et al. The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. *International journal of radiation oncology, biology, physics*. 2016;95(1):30-36.
35. Langendijk JA, Boersma LJ, Rasch CRN, et al. Clinical Trial Strategies to Compare Protons With Photons. *Seminars in radiation oncology*. 2018;28(2):79-87.
36. Gomez DR, Li H, Chang JY. Proton therapy for early-stage non-small cell lung cancer (NSCLC). *Translational lung cancer research*. 2018;7(2):199-204.
37. Verma V, Simone CB, 2nd. Approaches to stereotactic body radiation therapy for large (≥ 5 centimeter) non-small cell lung cancer. *Translational lung cancer research*. 2019;8(1):70-77.
38. Chen H, Senan S, Nossent EJ, et al. Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review. *International journal of radiation oncology, biology, physics*. 2017;98(3):622-631.
39. Naccache JM, Gibiot Q, Monnet I, et al. Lung cancer and interstitial lung disease: a literature review. *J Thorac Dis*. 2018;10(6):3829-3844.
40. Kim H, Pyo H, Noh JM, et al. Preliminary result of definitive radiotherapy in patients with non-small cell lung cancer who have underlying idiopathic pulmonary fibrosis: comparison between X-ray and proton therapy. *Radiation oncology*. 2019;14(1):19.
41. Chao HH, Berman AT. Proton therapy for thoracic reirradiation of non-small cell lung cancer. *Translational lung cancer research*. 2018;7(2):153-159.
42. Chao HH, Berman AT, Simone CB, 2nd, et al. Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2017;12(2):281-292.
43. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical Outcomes of Patients with Recurrent Lung Cancer Reirradiated with Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies. *Pract Radiat Oncol*. 2019.
44. Ho JC, Nguyen QN, Li H, et al. Reirradiation of thoracic cancers with intensity modulated proton therapy. *Pract Radiat Oncol*. 2018;8(1):58-65.
45. Kann BH, Miccio JA, Stahl JM, et al. Stereotactic body radiotherapy with adjuvant systemic therapy for early-stage non-small cell lung carcinoma: A multi-institutional analysis. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*. 2019;132:188-196.
46. Deslypere G, Gullentops D, Wauters E, Vansteenkiste J. Immunotherapy in non-metastatic non-small cell lung cancer: Can the benefits of stage IV therapy be translated into earlier stages? *Ther Adv Med Oncol*. 2018;10:1758835918772810.
47. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.
48. Scharping NE, Menk AV, Whetstone RD, Zeng X, Delgoffe GM. Efficacy of PD-1 Blockade Is Potentiated by Metformin-Induced Reduction of Tumor Hypoxia. *Cancer Immunol Res*. 2017;5(1):9-16.
49. Afzal MZ, Mercado RR, Shirai K. Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma. *J Immunother Cancer*. 2018;6(1):64.
50. Cha JH, Yang WH, Xia W, et al. Metformin Promotes Antitumor Immunity via Endoplasmic Reticulum-Associated Degradation of PD-L1. *Mol Cell*. 2018;71(4):606-620 e607.
51. Detterbeck FC. Pancoast (superior sulcus) tumors. *The Annals of thoracic surgery*. 1997;63(6):1810-1818.

52. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction Chemoradiation and Surgical Resection for Superior Sulcus Non-Small-Cell Lung Carcinomas: Long-Term Results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *Journal of Clinical Oncology*. 2007;25(3):313-318.
53. Buderl S, Shackcloth M, Woolley S. Does induction chemoradiotherapy increase survival in patients with Pancoast tumour? *Interactive cardiovascular and thoracic surgery*. 2016;23(5):821-825.
54. Kappers I, van Sandick JW, Burgers JA, et al. Results of combined modality treatment in patients with non-small-cell lung cancer of the superior sulcus and the rationale for surgical resection. *Eur J Cardiothorac Surg*. 2009;36(4):741-746.
55. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(suppl_4):iv1-iv21.
56. Lee HK, Vaporciyan AA, Cox JD, et al. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *International journal of radiation oncology, biology, physics*. 2003;57(5):1317-1322.
57. Takahashi S, Go T, Kasai Y, Yokomise H, Shibata T. Relationship between dose-volume parameters and pulmonary complications after neoadjuvant chemoradiotherapy followed by surgery for lung cancer. *Strahlenther Onkol*. 2016;192(9):658-667.

CHAPTER 9

Valorisation

VALORISATION

Relevance

Approximately half of the patients with non-small cell lung cancer have incurable stage IV disease at diagnosis. For stage I- III NSCLC the outcome is slightly better, but with a 5-year overall survival of 70% (stage I), 50% (stage II) or 20-40% (stage III), prognosis is still poor ^{1,2}. Efforts to improve the (effect of) currently available treatments have not lead to a substantial increase in the chance of curation. In the current thesis several studies were undertaken, aiming to improve the prospects of NSCLC patients.

In early stage NSCLC, we searched for significant risk factors for isolated regional recurrence and distant recurrence following SABR. We could not identify significant risk factors, despite a large cohort of patients. This is a relevant result, as it highlights the need for further research for possible predictive factors. These variables can be incorporated in prediction models and decision support systems, to help clinical decision making in this often heterogeneous population.

In the study on metformin use, we did not research a new, expensive and rare systemic agent. On the contrary, metformin is widely available as first choice oral treatment for type II diabetes. From a cost-effective standpoint, it is an attractive medication to repurpose for the treatment of cancer because it is very cheap. The pill costs only around 2 euros a month, versus approximately 5300 euros a month for two nivolumab infusions or 5700 euro for one pembrolizumab infusion, for example (www.farmacotherapeutischkompas.nl). In a retrospective study, we showed an improved progression free survival and distant metastasis free survival for locally advanced NSCLC patients using metformin during concurrent chemoradiotherapy ³. These results merit confirmation in a randomised controlled trial including non-diabetic patients. If confirmed, metformin could be added to the treatment of NSCLC without greatly increasing treatment costs, provided treatment related toxicity is not significantly increased.

Proton therapy is a sophisticated, innovative technique with the potential to reduce dose to organs at risk ⁴. The optimal clinical context for proton therapy for the treatment of NSCLC remains to be defined. As (comparative) clinical experience is limited, intermediate outcome measures are needed. Planning studies like the two we have performed are needed to specify the most relevant indications for this new technique.

Target groups

Non-small cell lung cancer patients (mainly stage I-III) are the most important target group of the current study. They may benefit directly or indirectly (in follow-up stud-

ies) from the results obtained in the current thesis. We showed that the addition of metformin to concurrent chemoradiotherapy has the potential to significantly improve prognosis for locally advanced NSCLC patients, although the results from prospective trials (NCT02186847 and NCT02115464) need to be awaited. Furthermore, clinicians in the field of pulmonary oncology and radiotherapy are likely to be interested in the results of our studies. The study on metformin received great attention at the IASLC World Lung Cancer Conference in Vienna in 2016, where the abstract was awarded with the Daniel C. Ihde Lectureship Award. Our results can also inspire other researchers in clinical practice or researchers working in the field of radiobiology or radiation technology. Examples include combining metformin with immunotherapy (pre-clinical and/or in clinical studies) or continuing and expanding the search for prognostic variables for recurrence following SABR.

Knowledge utilisation

Further research is needed before most of our results can be of use in clinical practice, as described in the ‘future perspectives’ section of the general discussion. The results we have obtained in the two retrospective observational studies (chapter 3 and chapter 4) can serve as a starting point for prospective trials. Both *in silico* trials are relevant for the specification of the best indications for proton therapy in NSCLC, as mentioned earlier. However, to evaluate the clinical efficacy and cost-effectiveness of this new technique, not only dosimetric data, but also clinical trials and modelling studies are essential⁵.

Innovation

Each of the studies in the current thesis has an innovative aspect. Using the pre-SABR planning CTs as surrogate for visceral pleural invasion was a unique feature of our study on regional recurrence following SABR. Repurposing the well-known and often prescribed anti-diabetic drug metformin for another indication, the treatment of NSCLC, is another form of innovation. In both the planning studies we performed within the ROCOCO consortium, the potential dosimetric advantages of innovative radiotherapy techniques as proton therapy and carbon-ion therapy were evaluated. Furthermore, the set-up and digital framework of these studies, with multiple international partners creating treatment plans with different modalities on the same patient datasets can also be considered innovative.

REFERENCES

1. Goldstraw P, Chansky K, Crowley J, 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.
2. Walraven I, van den Heuvel M, van Diessen 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):442-446.
3. Wink KC, Belderbos JS, Dieleman EM, et al. Improved progression free survival for patients with diabetes and locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy. *Radiother Oncol*. 2016;118(3):453-459.
4. Durante M, Orecchia R, Loeffler JS. Charged-particle therapy in cancer: clinical uses and future perspectives. *Nat Rev Clin Oncol*. 2017;14(8):483-495.
5. Lievens Y, Pijls-Johannesma M. Health economic controversy and cost-effectiveness of proton therapy. *Semin Radiat Oncol*. 2013;23(2):134-141.

Samenvatting

SAMENVATTING

De afgelopen decennia is er vooruitgang geboekt in de behandeluitkomst van het niet-kleincellig longcarcinoom (NSCLC) middels verbeterde systeemtherapie, geavanceerde operatie technieken en moderne radiotherapie technieken. Desondanks blijft de prognose matig, waarbij een groot deel van de patiënten binnen afzienbare termijn afstandsmetastasen ontwikkelt en aan de ziekte komt te overlijden. Bovendien kan de toxiciteit van de behandeling aanzienlijk zijn, vooral bij de behandeling van de (lokaal) gevorderde stadia. Het belangrijkste doel van dit proefschrift was het onderzoeken van diverse innovatieve strategieën om de aanpak en prognose van NSCLC te verbeteren, zonder toename van toxiciteit. Er werd onderzoek gedaan naar klierrecidieven na stereotactische ablatieve radiotherapie (SABR) voor beperkt stadium NSCLC, metformine gebruik tijdens concurrent chemoradiatie voor lokaal gevorderd NSCLC en deeltjesstraling voor een beperkt stadium en recidief NSCLC.

De standaard behandeling van een beperkt stadium niet-kleincellig longcarcinoom bestaat uit een resectie, meestal van de gehele longkwab waarin de tumor zich bevindt (een zogenaamde lobectomie). Daarbij worden ook hilaire en mediastinale lymfeklieren verwijderd, om te controleren op eventuele occulte lymfekliermetastasen. Voor patiënten die inoperabel zijn vanwege comorbiditeit of niet geopereerd willen worden, vormt SABR een goed alternatief. SABR bestaat uit hoog gedoseerde, zeer precieze bestraling in een beperkt aantal fracties. De beschreven lokale controle is >90%, wat vergelijkbaar is met operatieve behandeling. De bestraling wordt door patiënten meestal goed verdragen, zonder significante achteruitgang van de longfunctionaliteit (ook bij patiënten met een bij aanvang matige longfunctie) en kwaliteit van leven. Een verschil met operatieve behandeling is dat de lymfeklieren niet pathologisch geëvalueerd worden. In **hoofdstuk 2** beschrijven we in een systematische review van de beschikbare literatuur de incidentie van, en risicofactoren voor, het optreden van lymfekliermetastasen na SABR of chirurgie bij patiënten met een beperkt stadium niet-kleincellig longcarcinoom. De gerapporteerde gemiddelde incidentie van RR na SABR in de 16 geïnccludeerde studies was 9.6% (range 0-28.6%). Studies die regionale controle vergeleken tussen patiënten die SABR of resectie hadden ondergaan vonden een vergelijkbaar percentage lymfeklierrecidieven, ondanks de lymfeklierdissectie bij de geopereerde patiënten. Het niet behandelen van de lymfeklieren bij SABR lijkt dus niet te leiden tot meer regionale recidieven, hoewel dat wel vaak verwacht wordt. Mogelijke verklaringen die in de literatuur genoemd worden zijn 'toevallige' dosis in de lymfeklieren in de nabijheid van de bestraalde tumor (met als gevolg sterilisatie van micrometastasen), verschillen in follow-up en SABR patiënten zouden vaker overlijden als gevolg van aanwezige comorbiditeit (niet-kanker gerelateerd). De volgende risicofactoren voor het krijgen van een klierrecidief na SABR

worden beschreven: het mannelijk geslacht en een verlaagd hemoglobinegehalte in het bloed (anemie). Ook bleek 'toevallige' stralingsdosis hilar of mediastinaal van invloed: hoe hoger de dosis, hoe lager de regionale recidiefkans. In de chirurgische literatuur werden de volgende risicofactoren aangetoond: occulte kliermetastasering ten tijde van operatie, ingroei van de tumor in de viscerale pleura (het longvlies) oftewel viscerale pleurale invasie (VPI) en aanwezige tumorcellen in de bloed- en lymfvaten in de tumor (lymfovasculaire invasie). Een duidelijke subgroep van patiënten met een hoge kans op een lymfeklierrecidief kon echter niet gedefinieerd worden op basis van onze review. Het identificeren van patiënten met een hoog risico op occulte kliermetastasen en een (geïsoleerd) regionaal recidief is wenselijk om de diagnostische work-up van patiënten en de frequentie en uitgebreidheid van follow-up beter te sturen en te individualiseren. Dit is vooral relevant in geval van fitte, operabele patiënten die SABR verkiezen boven een operatie. Deze patiënten zijn potentieel fit genoeg om adjuvante systeemtherapie te ondergaan in geval van een hoog risico op een (loco)regionaal recidief en in opzet curatieve salvage behandeling als een recidief daadwerkelijk optreedt.

In **hoofdstuk 3** staan de resultaten beschreven van een retrospectief cohortonderzoek bij 554 patiënten die stereotactisch bestraald zijn voor een beperkt stadium niet-kleincellig longcarcinoom (stadium cT1-3N0M0). De primaire uitkomst die werd geëvalueerd is het optreden van een lymfeklierrecidief na SABR, zonder aanwijzingen voor metastasen op afstand (geïsoleerd regionaal recidief, IRR). Gekeken is naar de incidentie van IRR en eventuele voorspellende factoren. De prognostische waarde van de aanwezigheid en mate van contact van de tumor met de pleura (thoraxwand en fissuren) werd getest als surrogaat voor VPI. Hiervoor werd gebruik gemaakt van de computertomografie (CT) scans die waren vervaardigd ten behoeve van SABR planning. Bij 79% van de patiënten was sprake van contact van de tumor met de pleura, over een mediane lengte van 23mm. In totaal kon voor 494 patiënten gekeken worden naar de incidentie van IRR, welke 4% bedroeg (21/494). Gedurende de follow-up werden bij 91 patiënten (18%) metastasen op afstand geconstateerd. De cumulatieve incidentie van IRR en afstands-metastasen bedroegen na 1, 2 en 5 jaar respectievelijk 2%, 3%, 7% en 8%, 15% and 21%. De algehele overleving na 2 jaar bedroeg 71%. Van de patiënten met een IRR kreeg 43% palliatieve symptoombestrijding en slechts 33% radicale behandeling. Contact met de viscerale pleura bleek niet geassocieerd met een van de uitkomsten. Bij multivariate analyse correleerde het klinisch tumorstadium met het ontwikkelen van metastasen op afstand. Verder onderzoek naar risicofactoren voor occulte lymfekliermetastasen, lymfeklier recidieven, het ontstaan van afstandsmetastasen en overlijden is geïndiceerd. Voorspellende factoren kunnen geïntegreerd worden in predictiemodellen en gebruikt worden voor risico-gerichte diagnostiek, behandeling en follow-up na SABR.

In **hoofdstuk 4** hebben we bij patiënten met een lokaal gevorderd niet-kleincellig longcarcinoom onderzocht wat de invloed is van het gebruik van metformine (een veel gebruikt glucose verlagend middel bij diabetes mellitus) tijdens concurrent chemoradiatie. Van dit medicijn worden in diverse (pre-)klinische studies anti-kanker effecten beschreven bij diverse vormen van kanker, inclusief het niet-kleincellig longcarcinoom. Er werden 682 patiënten geïnccludeerd, waarvan 59 metformine gebruikten tijdens hun behandeling. Er waren geen significante verschillen tussen de controlegroep en metforminegroep wat betreft tumorgrootte en -stadium, conditie, geslacht, histologie of bestralingsdosis. De mediane leeftijd bij diagnose was 63 jaar en de patiënten waren meestal in een goede algehele conditie. Wel waren de patiënten die metformine gebruikten gemiddeld 7 jaar ouder ($p < 0.001$). De gemiddelde totale bestralingsdosis die werd gegeven bedroeg 66.1 Gy (range 50 – 129.6 Gy) in gemiddeld 31 fracties (range 19 – 45) van gemiddeld 2.3 Gy (range 1.2 – 5.4 Gy). Na een mediane follow-up van 18 maanden hadden 210 van alle patiënten (31%) een locoregionaal recidief ontwikkeld, waarvan 14 metformine gebruikten tijdens de behandeling (24%, $p = 0.15$). De mediane overleving bedroeg 33 maanden in de metforminegroep en 23 maanden in de controle groep ($p = 0.39$). De progressie-vrije overleving en overleving zonder metastasen op afstand was significant beter in de metforminegroep. Na twee jaar had 74% van de patiënten in de controlegroep en 53% van de patiënten in de metforminegroep afstandsmetastasen ontwikkeld ($p = 0.01$). De progressie-vrije overleving bedroeg na twee jaar 58% versus 37%, in het voordeel van de metforminegroep ($p = 0.01$). Metformine gebruik bleek bij multivariate analyse een significante onafhankelijke variabele voor de progressie-vrije overleving en overleving zonder metastasen op afstand. Onze bevindingen ondersteunen het belang van prospectieve (gerandomiseerde) trials naar het toevoegen van metformine aan de standaard behandeling van NSCLC.

Hoofdstuk 5, 6 en 7 in dit proefschrift hebben betrekking op de toepassing van deeltjesstraling met protonen of koolstof-ionen voor het niet-kleincellig longcarcinoom. De fysieke eigenschappen van straling met protonen of koolstof-ionen, vooral wat betreft dosisdistributie, kunnen ervoor zorgen dat gezonde weefsels rondom het doelgebied beter gespaard worden. In **hoofdstuk 5** worden de resultaten van een review naar de klinische uitkomsten en technische aspecten van het gebruik van deeltjesstraling voor de behandeling van beperkt en lokaal gevorderd NSCLC beschreven. Meerdere studies lieten een dosimetrisch voordeel zien voor protonen of koolstof-ionen in vergelijking met fotonen. De gerapporteerde klinische uitkomsten lijken voor alle ziektestadia overeen te komen met reeds bekende data over patiënten bestraald met fotonen. De toxiciteit is op zijn minst vergelijkbaar en mogelijk lager met deeltjes. In de meeste studies werd de inmiddels 'verouderde' passieve scatter techniek (PST) toegepast, gebruikt makend van collimators en compensators om het tumorvolume in zijn geheel te bestra-

len. Met de modernere ‘potloodbundel’ scanning techniek (PBS), wordt het doelvolumen punt-voor-punt gescand met een smalle protonenbundel, waardoor intensiteitsgemoduleerde protonentherapie mogelijk is (IMPT). Een mogelijk nadeel van IMPT is dat deze techniek gevoeliger is voor de ademhalingsbeweging dan de PST. De wisselwerking tussen de beweging van de tumor tijdens de bestraling (bijvoorbeeld met ademhaling) en de afgegeven potloodbundels kan bijvoorbeeld een nadelig effect hebben op de dosisverdeling: een bepaald punt in de tumor kan meerdere keren bestraald worden of steeds worden ‘overgeslagen’. Dit zogenaamde ‘wisselwerkingseffect’ kan leiden tot over- of onderdosering in het doelvolumen.

In **hoofdstuk 6** wordt de dosis in diverse risico organen en de mogelijkheden tot dosis escalatie vergeleken tussen diverse SABR technieken: intensiteitsgemoduleerde radiotherapie (IMRT), continue boogbestraling (volumetric arc therapy, VMAT), Cyberknife, PST of intensiteitsgemoduleerde koolstof-ionen (intensity modulated carbon-ion therapy, IMIT). Deze *in silico* studie werd uitgevoerd binnen het internationale ‘Radiation Oncology Collaborative Comparison’ (ROCO) consortium, gebruik makend van de planning CTs van 24 stereotactisch bestraalde patiënten. De voorgeschreven dosis was 60Gy in 8 fracties van 7,5Gy en de tumoren waren overwegend perifeer in de buurt van de thoraxwand gelegen. Gemiddeld was de dosis in de risico organen het laagst voor IMIT. De absolute dosis verlaging was echter beperkt, waarbij de klinische relevantie onduidelijk is. VMAT en Cyberknife resulteerden ook in betere sparing van de normale weefsels in vergelijking met IMRT. PST bleek te resulteren in een hogere dosis in de thoraxwand en de ribben vergeleken met IMRT en de conformaliteit liet te wensen over. Ook was PST de meest beperkende techniek voor dosisescalatie. Op basis van onze studie lijkt de toegevoegde waarde van bestraling met protonen of koolstof-ionen voor perifeer gelegen stadium I tumoren beperkt. De mogelijke voordelen zullen waarschijnlijk niet opwegen tegen de extra kosten voor deze state-of-the-art behandeling. Voor bepaalde subpopulaties met beperkt stadium NSCLC kunnen protonen of IMIT mogelijk wel voordelen bieden. Nader onderzoek kan worden overwogen bij patiënten met centrale tumoren (dichtbij kritieke structuren als centrale bloedvaten, hart of hoofdbronchus), grote tumoren, multipole tumoren of in geval van herbestraling.

De mogelijkheden met betrekking tot herbestraling hebben we onderzocht in **hoofdstuk 7**, opnieuw binnen het ROCOCO consortium. Voor elk van de 24 eerder bestraalde patiënten werden zeven bestralingsplannen gemaakt, elk met een van zeven verschillende bestralingstechnieken (VMAT, driedimensionale conformatie radiotherapie (3D-CRT), IMRT, tomotherapie, Cyberknife, PST en IMPT). Per casus waren individuele dosis constraints voor de risico organen beschikbaar, rekening houdend met de eerder ontvangen bestraling om de stralingstolerantie van de gezonde weefsels niet te over-

schrijden. Het ontbreken van intensiteitsmodulatie leidde bij 3D-CRT en PST tot meer concessie aan de dekking van het doelvolumen in vergelijking met de andere modaliteiten. De belangrijkste conclusie van de studie is dat met een vergelijkbare dekking van het doelgebied, de IMPT plannen resulteerden in een lagere gemiddelde dosis in hart en longen en minder uitwaaiing van lage dosis in de longen. De gemiddelde en maximum dosis in andere risico organen (bijvoorbeeld slokdarm, luchtwegen en mediastinale structuren) waren vergelijkbaar tussen de modaliteiten of iets beter met IMPT. Voorzichtigheid blijft wel geboden, want met een doelgebied dichtbij of overlappend met eerder bestraalde structuren kan ernstige toxiciteit optreden na re-irradiatie, ook met protonen.

In het huidige proefschrift werden diverse innovatieve strategieën geëxploreerd om de behandeling en daarmee de prognose van patiënten met stadium I-III niet-kleincellig longcarcinoom te verbeteren. Met dat doel voor ogen is het belangrijk om over- en onderbehandeling van patiënten te voorkomen door een individuele, patiënt gerichte aanpak. Predictiemodellen waarmee patiënten met de hoogste recidiefkans en/of kans op toxiciteit geïdentificeerd kunnen worden zijn essentieel om gepaste diagnostiek, therapie, adjuvante behandeling en follow-up in te zetten.

De optimale indicaties voor de behandeling van het niet-kleincellig longcarcinoom met protonen moeten verder gespecificeerd worden. Wat betreft de dosisdistributie zal IMPT gunstiger uitvallen in vergelijking met PST, mits voldoende rekening gehouden kan worden met de gevoeligheid van IMPT voor beweging en dichtheidsverschillen.

Dankwoord

DANKWOORD

Het zit erop! Mijn promotietraject is afgerond en het proefschrift is klaar! Veel personen hebben op de een of andere manier, direct of indirect, een bijdrage geleverd aan de totstandkoming van dit proefschrift. Hierbij wil ik een aantal van hen in het bijzonder bedanken.

Allereerst mijn oprechte dank aan mijn promotoren en copromotor, Esther Troost, Dirk de Ruyscher en Angela van Baardwijk.

Lieve Esther: bij jou is het allemaal begonnen. De enthousiaste en fijne begeleiding tijdens mijn wetenschapsstage en jouw passie voor de wetenschap werkten aanstekelijk. Na het vlotte schrijven en publiceren van ons eerste artikel hebben we de mogelijkheden voor een promotietraject verkend en gingen we van start. Toen nog met jou als copromotor. Toen je mij vertelde dat je van Maastricht naar Dresden zou vertrekken om daar als professor aan de slag te gaan, verzekerde je mij dat je mij zou blijven begeleiden tot aan de verdediging. Deze belofte heb je zeker gehouden! Ik denk dat er veel PhD-studenten zijn die minder hebben aan een promotor die dichtbij woont dan dat ik aan jou heb gehad. Ik ben je dan ook ontzettend dankbaar voor alle spoedige, nuttige en uitgebreide feedback per mail of in een van onze vele Skype gesprekken, je gastvrijheid en je geloof in mij. Dit heeft mij gesterkt en gemotiveerd en ik weet zeker dat ik zonder jou niet zover had kunnen komen. In jouw nieuwe functie werd je mijn promotor, samen met Dirk, en ik vind het heel speciaal dat ik jouw tweede promovenda mag zijn.

Dirk: ook jij bedankt voor de fijne begeleiding. Met jouw ervaring, kennis en reputatie in het veld van de longoncologie prijs ik mij zeer gelukkig dat je een bijdrage hebt willen leveren aan mijn proefschrift. Jouw literatuurkennis en ideeën waren onmisbaar voor mijn onderzoek. Ik heb veel geleerd van onze inhoudelijke gesprekken over de diverse onderwerpen in mijn proefschrift, waarbij ik mij steeds weer heb verwonderd over hoe feilloos jij percentages en getallen uit recente en niet-recent gepubliceerde literatuur weet te reproduceren.

Mijn copromotor, Angela van Baardwijk, wil ik ook van harte bedanken. Toen bleek dat Esther naar Dresden ging was er een nieuwe copromotor nodig bij MAASTRO clinic. Als mijn opleider destijds heb jij deze taak op je genomen en heb je er samen met Esther voor gezorgd dat ik na afronden van mijn opleiding een jaar full-time aan mijn proefschrift kon werken. Ik ben je heel dankbaar voor je inzet, je nuttige inhoudelijke suggesties en ook je interesse in mij op werk en privégebied, ook na afronden van mijn opleiding.

Graag zou ik ook de leden van de beoordelingscommissie, professor Anne-Marie Dingemans, professor Liesbeth Boersma, professor Piet Postmus en Antje Knopf willen bedanken voor het beoordelen van mijn proefschrift en de bereidheid plaats te nemen in de promotiecommissie.

Voor mijn onderzoek heb ik met diverse personen samen gewerkt, bij MAASTRO clinic en daarbuiten. Erik Roelofs: bedankt voor de vele uren (vaak ook thuis) die je hebt gestoken in het ROCOCO project. Dit grote, internationale project was een uitdaging, to say the least, maar uiteindelijk is het af en is het iets om trots op te zijn. Judith van der Stoep bedankt voor de mooie planningen en Esther Bloemen voor de protocollen en logistieke werkzaamheden. Ook ben ik de deelnemende partners (nationaal en internationaal) zeer dankbaar voor hun medewerking.

Ruud Houben (MAASTRO) en Steffen Löck (Dresden) thank you for your knowledge and skills with respect to statistical analyses! You were a great help.

Voor het onderzoek naar klierrecidieven na stereotaxie heb ik vele uren metingen gedaan in het Antoni van Leeuwenhoek. Maddalena: bedankt voor je harde werk aan de database, je snelle reactie op mijn mails en je gezelligheid! Ook José Belderbos bedankt voor de prettige samenwerking, kritische blik en nuttige aanvullingen bij dit project maar ook dat over metformine. Ook alle andere coauteurs die ik nog niet bij naam genoemd heb: dank voor alle input!

Ook niet te vergeten: Mariëlle Vincken, je bent een topper! Heel erg bedankt dat je de secretariële ondersteuning rondom de goedkeuring van mijn promotie, het plannen van de datum en alle papieren rompslomp op je hebt willen nemen. Zo fijn dat dit zo goed, snel en met enthousiasme geregeld werd, dit heeft mij veel stress gescheeld! Bedankt!

Inmiddels werk ik alweer ruim 2 jaar met veel plezier als radiotherapeut-oncoloog in het Leids Universitair Medisch Centrum en het Reinier de Graaf Gasthuis in Delft. Bedankt lieve (oud-)collega's voor de fijne werkomgeving en jullie steun de afgelopen jaren!

Om een promotietraject af te kunnen ronden kan de boog niet altijd gespannen zijn. Ontspanning en afleiding is een must en gelukkig heb ik veel lieve vrienden en vriendinnen die daarvoor hebben kunnen zorgen. Mijn oude studie vrienden en hun partners: Loes en Gideon, Philip en Charlotte en Manon en Arthur. Zo leuk dat we nog steeds contact hebben ondanks dat we inmiddels verspreid over het land wonen. Loes en Philip: heel erg bedankt dat jullie mijn paranimfen willen zijn.

Mijn Eindhovense tennis vriendinnetjes Marjon, Ilse, Irene, Marijke, Kim, Laurie en Stephanie. Zo jammer dat we niet meer samen competitie tennissen, maar de borrel avonden en weekendjes weg (en inmiddels speeluitjes met de kids) zou ik nooit willen missen. Volgend jaar weer naar Ibiza? Oud Stennis vriendinnetjes Kim, Mignon en Vivian, oud AIOS-collega Miranda, oud-klasgenootjes Annemarie en Carlyn: ook jullie bedankt!

Mijn familie is ook ontzettend belangrijk geweest bij de totstandkoming van dit proefschrift. Pap en mam: jullie zijn geweldig! Jullie hebben mij altijd gesteund en altijd interesse getoond in mijn werkzaamheden en mij vaak laten weten hoe trots jullie zijn. Ook even oppassen op Roan zodat ik even kon werken was zelden een probleem. Jullie hebben allebei flink getobd met jullie gezondheid de afgelopen 1,5 jaar. Desondanks kon ik altijd bij jullie terecht en heb ik heel veel aan jullie gehad. Heel erg bedankt voor alles.

Lieve Suzanne, Suus, 'kleine' zus. Je woont al een hele tijd in Australië en hebt het hier erg naar je zin. Ik vind het heel fijn dat we regelmatig Skypen om bij te kletsen, maar dat je als het nodig is het vliegtuig instapt om er te zijn voor je familie en je vrienden. Ik vind het dan ook heel speciaal en fijn dat je bij mijn verdediging zal zijn! Dankjewel!

Lieve oma Wink, u bent niet meer in ons midden, maar toch wil ik u in het bijzonder hier noemen. Op 23 juli 2018 overleed u op 88 jarige leeftijd aan verraderlijke de ziekte die ik dagelijks behandel en waar ik mijn proefschrift aan gewijd hebt. We werden allemaal verrast toen u ineens zo ontzettend ziek werd. Amper een maand na de diagnose longkanker bent u overleden. U rookte niet, was altijd sterk, weinig ziek en mantelzorger voor opa. We missen u, wij als gezin en vooral ook opa, met wie u al meer dan 70 jaar samen was. Helaas heeft u de geboorte van onze zoon Roan in oktober 2018 en de verdediging van mijn proefschrift niet meer mogen meemaken. Ik ben heel trots op dat ik dit waardevolle onderzoek heb mogen doen en hopelijk in de toekomst nog veel voor longkanker patiënten kan betekenen, klinisch, maar vooral ook op het gebied van wetenschappelijk onderzoek. Hierbij zult u vaak in mijn gedachten zijn.

Mijn opa Wink en mijn schoonfamilie wil ik ook van harte bedanken voor de oprechte interesse in (de voortgang van) mijn promotieonderzoek. Een speciaal bedankje ook voor mijn zwager Lars, voor het ontwerpen van de 'innovatieve' kaft van dit proefschrift.

Lieve Roan, je bent nog te klein om het allemaal te beseffen, maar wat ben ik ontzettend gelukkig met jou! Jouw vrolijkheid, gezelligheid en knuffels hebben voor de nodige positieve afleiding en energie gezorgd als ik het even niet meer zag zitten. Ook heb je me al heel snel mijn nachtrust gegund zodat ik overdag genoeg energie had voor het

schrijven. Je hebt me leren relativeren en in laten zien dat er meer is dan werken alleen, dankjewel lieve schat!

Tot slot, Odin, mijn houvast en mijn grote liefde. Zonder jou was het me nooit gelukt dit voor elkaar te krijgen. Ook jouw knuffels en bemoedigende woorden hebben me ontzettend geholpen. Ook jij hebt veel moeten laten schieten zodat ik dit traject succesvol kon afronden en ik ben je heel erg dankbaar. Nu zijn de avonden en weekenden weer van ons en daar gaan we van genieten!

Curriculum Vitae

CURRICULUM VITAE

Krista Wink werd geboren op 30 juni 1986 in Nijmegen. Na het atheneum aan College de Heemlanden in Houten, startte zij in 2004 met de opleiding Geneeskunde aan de Universiteit van Maastricht. In 2010 behaalde zij haar Master of Science in Geneeskunde, waarna ze in 2011 begon als arts in opleiding tot radiotherapeut-oncoloog bij MAASTRO clinic in Maastricht (opleiders dr. J. Jager, dr. A.A.W. van Baardwijk en dr. K.E.A. de Jaeger). Gedurende de opleiding, met name tijdens de wetenschapsstage in 2014 onder begeleiding van professor E.G.C. Troost, werd haar interesse voor de wetenschap en de specialisatie (niet-kleincellig) longcarcinoom gewekt. Vanuit deze stage werd het promotietraject opgestart dat heeft geresulteerd in het huidige proefschrift. Na het afronden van de opleiding in 2016 volgde een jaar full time onderzoek en werkte ze enkele maanden als waarnemer bij MAASTRO clinic. Sinds juni 2017 is ze als lid van de medische staf verbonden aan de afdelingen radiotherapie in het Leids Universitair Medisch Centrum en het Reinier de Graaf Gasthuis in Delft.

Publications and grants

PUBLICATIONS

Wink, K. C. J., S. Lock, M. Rossi, A. van Baardwijk, J. Belderbos, D. de Ruyscher, and E. G. C. Troost. "Contact of a Tumour with the Pleura Is Not Associated with Regional Recurrence Following Stereotactic Ablative Radiotherapy for Early Stage Non-Small Cell Lung Cancer." *Radiother Oncol* 131 (Feb 2019): 120-26.

Wink, K. C. J., E. Roelofs, C. B. Simone, 2nd, D. Dechambre, A. Santiago, J. van der Stoep, W. Dries, J. Smits, S. Avery, F. Ammazalorso, N. Jansen, U. Jelen, T. Solberg, D. de Ruyscher, and E. G. C. Troost. "Photons, Protons or Carbon Ions for Stage I Non-Small Cell Lung Cancer - Results of the Multicentric Rococo in Silico Study." *Radiother Oncol* 128, no. 1 (Jul 2018): 139-46.

Wink, K. C. J., A. van Baardwijk, E. G. C. Troost, and D. De Ruyscher. "Nodal Recurrence after Stereotactic Body Radiotherapy for Early Stage Non-Small Cell Lung Cancer: Incidence and Proposed Risk Factors." *Cancer Treat Rev* 56 (May 2017): 8-15.

Wink, K. C. J., S. Belderbos, E. M. Dieleman, M. Rossi, C. R. Rasch, R. A. Damhuis, R. M. Houben, and E. G. Troost. "Improved Progression Free Survival for Patients with Diabetes and Locally Advanced Non-Small Cell Lung Cancer (Nslc) Using Metformin During Concurrent Chemoradiotherapy." *Radiother Oncol* 118, no. 3 (Mar 2016): 453-9.

Wink, K. C. J., E. Roelofs, T. Solberg, L. Lin, C. B. Simone, 2nd, A. Jakobi, C. Richter, P. Lambin, and E. G. Troost. "Particle Therapy for Non-Small Cell Lung Tumors: Where Do We Stand? A Systematic Review of the Literature." *Front Oncol* 4 (2014): 292.

Wink, K. C. J., K. Woensdregt, G. A. Nieuwenhuijzen, M. J. van der Sangen, S. Hutsche-maekers, J. A. Roukema, V. C. Tjan-Heijnen, and A. C. Voogd. "Hormone Treatment without Surgery for Patients Aged 75 Years or Older with Operable Breast Cancer." *Ann Surg Oncol* 19, no. 4 (Apr 2012): 1185-91.

Troost E. G. C., **K. C. J. Wink**, E. Roelofs, C. B. Simone, 2nd, S. Makocki, S. Löck, P. van Kol-lenburg, D. Dechambre, A. W. H. Minken, J. van der Stoep, S. Avery, N. Jansen, T. Solberg, J. Bussink, D. de Ruyscher "Photons or protons for re-irradiation in (non-)small cell lung cancer? Results of the multicentric ROCOCO in silico study." Submitted.

BOOK CHAPTERS

E.G.C. Troost, **K. C. J. Wink**, J. D. Zindler, D. de Ruyscher. "Management of early stage lung cancer – perspective of a radiation oncologist." Hoofdstuk in boek '*Lung Cancer*', editors A. C. Dingemans, M. Reck, en V. Westeel, published in May 2015 (ERS Monograph).

GRANTS

- 2014 **René Vogels travel grant**, for an internship at the Heidelberg Iontherapy Center (HIT) and Centre de Protontherapie d'Orsay (CPO) for a month in May 2014
- 2016 **IASLC Young Investigator's Travel Award and Daniel C. Ihde Lectureship Award** for abstract '*Improved progression free survival for diabetic patients with locally advanced non-small cell lung cancer (NSCLC) using metformin during concurrent chemoradiotherapy*,' presented at the IASLC 17th World Conference on Lung Cancer, December 2016, Vienna