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Motion monitoring for moving targets treated with pencil beam scanned proton therapy

den Otter, Lydia

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Lydia Anneke den Otter

Colofon

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Prof. dr. S. Both

Prof. dr. J.A. Langendijk

Beoordelingscommissie

Prof. dr. S. Brandenburg

Prof. dr. F. Verhaegen

Prof. dr. D. De Ruysscher

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Chapter 1

General introduction

Introduction

In the Netherlands, the incidence of cancer is still rising with more than 117,000 new cases in 2019 [1]. More than 2,500 and 10,000 patients were diagnosed with esophageal cancer and non-small cell lung cancer (NSCLC), respectively [1]. The overall survival of NSCLC varies widely with tumour stage. Among patients treated between 2010 and 2017, the 3-year overall survival for NSCLC in the Netherlands was 73% (stage I), 52% (stage II), 27% (stage III) and 6% (stage IV), respectively [1]. For stage I-III tumours, 47%, 25% and 60% of the patients received radiotherapy as part of treatment in 2017 [2, 3]. The outcome of treatment has improved over the last decades due to the introduction of chemotherapy, targeted agents and immunotherapy as well as by technological improvements in radiotherapy [4–7]. For example, recent publications showed that immunotherapy treatment with Durvalumab improved overall survival for non-resectable stage III NSCLC that first received chemoradiation (3-year overall survival 57.0% compared to 43.5%) [4, 5]. Stereotactic radiotherapy is an example of a technological advancement that can improve local control for inoperable peripheral stage I NSCLC [6].

In the Netherlands, the 3-year overall survival in esophageal cancer patients treated between 2010 and 2017 was 67% (stage I), 46% (stage II), 34% (stage III) and 3% (stage IV), respectively. The current standard approach in resectable esophageal cancer is neoadjuvant chemoradiation followed by surgery or definitive chemoradiation in case of irresectable locoregional disease [2, 8–12]. The current standard in resectable patients is based on the results of the ChemoRadiotherapy for Oesophageal cancer followed by Surgery Study (CROSS), a randomized controlled trial comparing surgery alone versus neoadjuvant chemoradiation followed by surgery. In this study, the 3-year overall survival improved from 44% with surgery alone to 58% with neoadjuvant chemoradiation followed by surgery [12].

Intensity-modulated radiation therapy (IMRT) is an advanced and conformal type of external beam radiation. IMRT uses dynamic multi-leaf collimators to modulate the beam intensities of multiple static fields and the corresponding

photon plans are calculated using the concept of inverse treatment planning [13, 14]. In this way, conformal treatment plans can be generated with complex dose distributions. Volumetric modulated arc therapy (VMAT) can be considered as a type of IMRT, where the gantry is continuously rotating around the patient and modulating the treatment beam [15]. For both esophageal cancer and NSCLC treatment, VMAT has become the current standard technique for photon radiotherapy at UMCG. The main advantage of VMAT compared to IMRT is that the treatment delivery has become faster, and thus more efficient [16–18].

The current state-of-the-art proton therapy technology is pencil beam scanning proton therapy (PBS-PT), which has recently become available as a treatment modality in the Netherlands. PBS is also available at UMCG at the Groningen Proton Therapy Center (GPTC). Protons deposit the majority of their kinetic energy while traveling through matter at the end of their range, defined as the so-called Bragg peak (Fig. 1) [19–22]. Negligible dose is deposited after the Bragg peak (sharp distal dose fall-off, Fig. 1), where photons deposit most of their energy near the entrance of the body and continue to travel through matter releasing their energy following a gradual linear decrease (Fig. 1).

Figure 1. Photon vs. proton beam depth-dose profiles. The green curve depicts a typical 15 MV photon beam. The red curve shows a monoenergetic proton beam.

The sharp distal dose fall-off is exploited with proton therapy to reduce the dose to healthy tissues. The range depends on the initial energy of the protons and the density of the material through which the protons travel. Furthermore, scanning magnets adjust the position of the monoenergetic pencil-beams in the x- and y-directions. PBS-PT can therefore be combined with intensity modulation technique as optimization strategy (intensity modulated proton therapy [IMPT]) to create highly conformal treatment plans [23, 24]. For NSCLC and esophageal cancer, PBS-PT can increasingly spare healthy tissue and reduce the dose to critical organs, compared to IMRT or VMAT treatments (Fig. 2) [25–29]. Fig. 2 illustrates for two representative cases that a more conformal dose distribution can be achieved for the IMPT treatments, in addition to the lower integral dose. This resulted in a mean heart dose reduction of 13.3 Gy (NSCLC case) and 8.1 Gy (esophageal cancer case).

Moving targets

Although, PBS-PT can be beneficial to many patients due to the superior physics of the beam and full automation, PBS beams have a time structure and are therefore more sensitive to motion. NSCLC and esophageal cancer are both regarded as moving targets, due largely to respiratory motion [30–33]. Cardiac motion and peristalsis of the esophagus are two other types of high frequency intra-fractional motion [31, 32, 34]. Furthermore, relaxation of the patient during treatment and variations in breathing motion and diaphragm position during and between treatment fractions should also be considered [29, 32, 34, 35]. Additionally, anatomical changes such as pleural effusion, (resolving) atelectasis, gastric and bowel filling variations, mediastinal deformations and target volume changes may also affect PBS-PT treatment, [29, 34, 36–42]. All these motion types can influence the breathing motion and cause target deformations and displacements, and also cause tissue density changes along the beam paths [43, 44]. For PBS-PT specifically, interplay effects can occur due to the relative motion between the scanned beam delivery and the moving target [30, 34, 45–48]. Without taking preventative measures, the dose distribution can be affected risking the target dose coverage being compromised and/or an increase of the dose to healthy tissues and critical organs, for example by under- or

overshooting the target at the distal edge [34, 43]. Proximally and laterally of the target volume, the conformity might be decreased with blurring of the dose distribution [45, 49, 50]. Furthermore, dose heterogeneities can occur resulting in unwanted hot- and cold spots [45, 46, 51–53].

A

B

Figure 2. Axial, coronal and sagittal views of VMAT and IMPT treatment plans (nominal dose distributions) for a sample NSCLC (A) and an esophageal cancer (B) case. The red contour represents the planning target volume (PTV) and the blue contour the internal clinical target volume (iCTV) for the VMAT and IMPT plans, respectively.

Motion monitoring

Many techniques and strategies have been developed to manage motion and anatomical changes during the course of treatment. These strategies can be divided into three categories: motion monitoring, motion mitigation and improving the robustness of proton therapy treatment to motion. Motion monitoring is important in order to gain insight into motion characteristics at the planning stage, and secondly to evaluate and observe changes in motion during the course of treatment. In many proton therapy centres, respiratory-correlated CT imaging (4DCT) has been integrated into the treatment planning workflow for moving targets [54–57]. Other centres also perform (weekly) repeated 4DCT imaging to evaluate the need for plan adaptation [29, 57–59]. 4DCT imaging offers relatively high-quality images of both the moving target and surrounding tissues. However, 4DCT imaging is susceptible to breathing irregularities that induce image artefacts and the 4DCT images only offer snapshots of the motion [55, 60]. Cone beam CT imaging has been adopted in recent years by a number of proton therapy centres for daily treatment alignment allowing for internal anatomy verification [61, 62]. Recently, the potential of 4DCBCT imaging is investigated for proton dose evaluation and it is expected that 4DCBCT will be implemented in the near future [63].

Motion mitigation

Motion mitigation techniques can be effectively applied in proton therapy for moving targets to reduce respiratory motion amplitudes. Abdominal compression has shown to limit liver, diaphragm and lower lobe lung motion, but should be combined with careful gantry angle selection in order to keep the proton beams from going through the device [30, 53, 64]. Breath-holding is also effective in mitigating respiratory motion and it can be done voluntarily or assisted [65–68]. However, one should be aware of the reproducibility of breath-holding and baseline shifts that may occur [66, 67, 69]. Gating is another motion mitigation technique where the treatment is only given during a gating window of motion to mitigate the respiratory motion [70–72]. Internal or external surrogate motion is monitored that should correlate well with the target motion [70–72]. The main

disadvantage of gating is the prolonged treatment time and therefore motion mitigation strategies are investigated with limited increase of treatment delivery times during treatment [70, 71, 73, 74]. Tumour tracking during treatment has been applied for photon treatments successfully [75–78]. However, for PBS-PT this technique is still under development. The main challenges are continuous adaptation to changes in radiological path lengths and accurate real-time motion monitoring of both target and surrounding moving structures [79–82]. Overall, for most motion mitigation techniques, residual motion remains and therefore other techniques have to be applied additionally to create a safe and robust PBS-PT treatment [73, 82–85].

Treatment robustness to motion

Increasing the robustness of PBS-PT treatment to motion has been investigated and implemented in many ways. A few techniques will be discussed here. First, from the perspective of motion, the beam angles should be chosen parallel to the largest direction of motion whenever possible [48, 86, 87]. Secondly, rescanning is an effective technique where each planned proton spot is delivered multiple times to average the dose heterogeneities caused by interplay effects [51, 86–89]. Different rescanning types have been investigated. Iso-layered rescanning, for example, is an approach where each spot is delivered with a maximum dose as limit and consequently the number of rescans will differ per spot [88]. Scaled rescanning is another approach that is also applied at GPTC (IBA Proteus©Plus machine, Louvain-la-Neuve, Belgium). With scaled (or controlled) rescanning, the prescribed dose to each spot is equally distributed over the number of rescans [87]. Rescanning can be performed volumetrically, which means that the complete target volume is scanned every rescanning cycle [86]. Layered rescanning is the other technique where the complete treatment fraction is delivered energy layer by energy layer [87]. 4D robust optimization includes multiple 4DCT phases during treatment planning and therefore accounts for the respiratory motion and anatomy as imaged by the 4DCT [90–94]. Furthermore, robust optimization is considered a requirement for PBS-PT treatment planning, as conventional geometric margins that are used for photon treatments are not sufficient due to the

range uncertainty [95]. Robust optimization incorporates uncertainties of both setup and range which improves both the target coverage and OARs sparing [96–99].

Outline thesis

The overarching aim of this thesis was to evaluate the need for motion monitoring of moving targets and nearby structures that are treated with PBS-PT. Furthermore, a 4DCBCT reconstruction method for daily motion monitoring was investigated for NSCLC patients. The outcomes of this research are important steps towards a safe implementation of PBS-PT for moving targets and can be read in the following chapters:

- **Chapter 2** evaluates the reproducibility of the lung anatomy under active breathing coordinator control. It addresses the possible dosimetric consequences when treating NSCLC with robust optimized PBS-PT, where respiratory motion is actively mitigated using breath-holding. In addition, we investigated whether this can be safely done or if additional monitoring or motion mitigation techniques are required.
- **Chapter 3** focuses on the inter-fraction target motion and target motion variability during free breathing radiotherapy treatment for a larger cohort of (N)SCLC patients. It addresses the need of weekly and daily motion monitoring in the context of PBS-PT treatment for these moving targets.
- **Chapter 4** investigates and reports on 4DCBCT reconstruction for moving targets to monitor motion on a daily basis. It focuses on the use of daily acquired sparse-view CBCT data to reconstruct 4DCBCT images of sufficient image quality for daily motion assessment.
- **Chapter 5** addresses the impact of diaphragm position variations on PBS-PT treatment and the need of daily diaphragm position monitoring and correction through 3DCBCT imaging.

The findings that are presented in this thesis will be summarized and discussed in chapter 6.

References

1. IKNL. NKR-cijfers. 2020. URL: <https://www.iknl.nl/nkr-cijfers> (visited on 09/28/2020).
2. IKNL. Kankersoorten. 2020. URL: <https://www.iknl.nl/kankersoorten> (visited on 09/28/2020).
3. IKNL. Oncoline - niet kleincellig longcarcinoom. 2015. URL: <https://www.oncoline.nl/niet-kleincellig-longcarcinoom> (visited on 09/28/2020).
4. Desilets A, Blanc-Durand F, Lau S, et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III nonsmall cell lung cancer: A real-world multicentre study. *Eur J Cancer* 2021;142:83–91.
5. Gray JE, Villegas A, Daniel D, et al. Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC Update from PACIFIC. *J Thor Onc* 2020;15:288–93.
6. 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. *Lancet Oncol* 2019;20:494–503.
7. Furuse BK, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, and Kudoh S. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with Mitomycin, Vindesine, and Cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–9.
8. IKNL. Oncoline - oesofaguscarcinoom. 2014. URL: <https://www.oncoline.nl/oesofaguscarcinoom> (visited on 09/28/2020).
9. Jin HL, Zhu H, Ling TS, Zhang HJ, and Shi RH. Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: A meta-analysis. *World J Gastroentero* 2009;15:5983–91.
10. Fiorica F, Di Bona D, Schepis F, et al. Preoperative chemoradiotherapy for oesophageal cancer: A systematic review and meta-analysis. *Gut* 2004;53:925–30.
11. Van Hagen P, Hulshof MC, Van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074–84.
12. Shapiro J, Lanschot J van, Hulshof C, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *Lancet Oncol* 2015;16:1090–8.

13. Bortfeld T. IMRT: A review and preview. *Phys Med Biol* 2006;51.
14. Kallman P, Lind B, Eklof A, and Brahme A. Shaping of arbitrary dose distributions by dynamic multileaf collimation. *Phys Med Biol* 1988;33:1291–300.
15. Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. *Med Phys* 2008;35:310–7.
16. Hawkins MA, Bedford JL, Warrington AP, and Tait DM. Volumetric modulated arc therapy planning for distal oesophageal malignancies. *Br J Radiol* 2012;85:44–52.
17. Lin CY, Huang WY, Jen YM, et al. Dosimetric and efficiency comparison of high-dose radiotherapy for esophageal cancer: Volumetric modulated arc therapy versus fixed-field intensity-modulated radiotherapy. *Dis Esophagus* 2014;27:585–90.
18. Quan EM, Chang JY, Liao Z, et al. Automated VMAT treatment planning for stage III lung cancer. *Int J Radiat Oncol Biol Phys* 2012;84:1–14.
19. Wilson RR. Radiological use of fast protons. *Radiology* 1946;47:487–91.
20. Berman A, James S, and Rengan R. Proton beam therapy for non-small cell lung cancer: current clinical evidence and future directions. *Cancers* 2015;7:1178–90.
21. Schulz-Ertner D and Tsujii H. Particle radiation therapy using proton and heavier ion beams. *J Clin Oncol* 2007;25:953–64.
22. Mohan R, Mahajan A, and Minsky BD. New strategies in radiation therapy: Exploiting the full potential of protons. *Clin Cancer Res* 2013;19:6338–43.
23. Lomax AJ. Physics in Medicine & Biology Related content Intensity modulation methods for proton radiotherapy. *Phys Med Biol* 1999;44:185–205.
24. Oelfke U and Bortfeld T. Intensity modulated radiotherapy with charged particle beams: Studies of inverse treatment planning for rotation therapy. *Med Phys* 2000;27:1246–57.
25. Liu C, Sio TT, Deng W, et al. Small-spot intensity-modulated proton therapy and volumetric-modulated arc therapies for patients with locally advanced non-small-cell lung cancer : A dosimetric comparative study. *J Appl Clin Med Phys* 2018;19:140–8.
26. Zhang X, Li Y, Xiaoning P, 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. *Int J Radiat Oncol Biol Phys* 2010;77:357–66.

27. Laan HP van der, Anakotta RM, Korevaar EW, et al. Organ sparing potential and inter-fraction robustness of adaptive intensity modulated proton therapy for lung cancer. *Acta Oncol* 2019;0:1–8.
28. Liu C, Bhangoo RS, Sio TT, et al. Dosimetric comparison of distal esophageal carcinoma plans for patients treated with small-spot intensity-modulated proton versus volumetric-modulated arc therapies. *J Appl Clin Med Phys* 2019;20:15–27.
29. Anakotta RM, Laan HP van der, Visser S, et al. Weekly robustness evaluation of intensity-modulated proton therapy for oesophageal cancer. *Radiother Oncol* 2020;151:66–72.
30. Bert C and Durante M. Motion in radiotherapy: particle therapy. *Phys Med Biol* 2011;56:113–44.
31. Hashimoto T, Shirato H, Kato M, et al. Real-time monitoring of a digestive tract marker to reduce adverse effects of moving organs at risk (OAR) in radiotherapy for thoracic and abdominal tumors. *Int J Radiat Oncol Biol Phys* 2005;61:1559–64.
32. Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–34.
33. Jin P, Hulshof MCCM, Jong R de, Hooft JE van, Bel A, and Alderliesten T. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. *Radiother Oncol* 2016;118:492–7.
34. Lomax A. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. *Phys Med Biol* 2008;53:1043–56.
35. Dhont J, Vandemeulebroucke J, Burghellea M, et al. The long- and short-term variability of breathing induced tumor motion in lung and liver over the course of a radiotherapy treatment. 2018.
36. Kwint M, Conijn S, Schaake E, et al. Intra thoracic anatomical changes in lung cancer patients during the course of radiotherapy. *Radiother Oncol* 2014;113:392–7.
37. Britton KR, Starkschall G, Tucker SL, et al. Assessment of gross tumor volume regression and motion changes during radiotherapy for non-small-cell lung cancer as measured by four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys* 2007;68:1036–46.

38. Fox J, Ford E, Redmond K, Zhou J, Wong J, and Song DY. Quantification of Tumor Volume Changes During Radiotherapy for Non-Small-Cell Lung Cancer. *Int J Radiat Oncol Biol Phys* 2009;74:341–8.
39. Bouchard M, McAleer MF, and Starkschall G. Impact of Gastric Filling on Radiation Dose Delivered to Gastroesophageal Junction Tumors. *Int J Radiat Oncol Biol Phys* 2010;77:292–300.
40. Nyeng TB, Nordsmark M, and Hoffmann L. Dosimetric evaluation of anatomical changes during treatment to identify criteria for adaptive radiotherapy in oesophageal cancer patients. *Acta Oncol* 2015;54:1467–73.
41. Yamashita H, Haga A, Hayakawa Y, et al. Patient setup error and day-to-day esophageal motion error analyzed by cone-beam computed tomography in radiation therapy. *Acta Oncol* 2010;49:485–90.
42. Møller DS, Alber M, Nordsmark M, Nyeng TB, Lutz CM, and Hoffmann L. Validation of a robust strategy for proton spot scanning for oesophageal cancer in the presence of anatomical changes. *Radiother Oncol* 2019;131:174–8.
43. Mori S, Wolfgang J, Lu HM, Schneider R, Choi NC, and Chen GT. Quantitative Assessment of Range Fluctuations in Charged Particle Lung Irradiation. *Int J Radiat Oncol Biol Phys* 2008;70:253–61.
44. Mori S and Chen GT. Quantification and Visualization of Charged Particle Range Variations. *Int J Radiat Oncol Biol Phys* 2008;72:268–77.
45. Bert C, Grözinger SO, and Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Phys Med Biol* 2008;53:2253–65.
46. 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. *Int J Radiat Oncol Biol Phys* 2013;86:380–6.
47. Kraus K, Heath E, and Oelfke U. Dosimetric consequences of tumour motion due to respiration for a scanned proton beam. *Phys Med Biol* 2011;56:6563–81.
48. Kang M, Huang S, Solberg TD, et al. A study of the beam-specific interplay effect in proton pencil beam scanning delivery in lung cancer. *Acta Oncol* 2017;56:531–40.
49. Bortfeld T, Jiang SB, and Rietzel E. Effects of Motion on the Total Dose Distribution. *Semin Radiat Oncol* 2004;14:41–51.
50. Protik A, Herk M van, Witte M, and Sonke JJ. The impact of breathing amplitude on dose homogeneity in intensity modulated proton therapy. *Phys Imag Radiat Oncol* 2017;3:11–6.

51. Phillips MH, Pedroni E, Blattmann H, Boehringer T, Coray A, and Scheib S. Effects of respiratory motion on dose uniformity with a charged particle scanning method. *Phys Med Biol* 1992;37:223–34.
52. Lambert J, Suchowerska N, McKenzie DR, and Jackson M. Intrafractional motion during proton beam scanning. *Phys Med Biol* 2005;50:4853–62.
53. Lin L, Souris K, Kang M, et al. Evaluation of motion mitigation using abdominal compression in the clinical implementation of pencil beam scanning proton therapy of liver tumors. *Med Phys* 2017;44:703–12.
54. Kang Y, Zhang X, Chang JY, et al. 4D Proton treatment planning strategy for mobile lung tumors. *Int J Radiat Oncol Biol Phys* 2007;67:906–14.
55. Trnková P, Knäusel B, Actis O, et al. Clinical implementations of 4D pencil beam scanned particle therapy: Report on the 4D treatment planning workshop 2016 and 2017. *Phys Med* 2018;54:121–30.
56. 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. *J Appl Clin Med Phys* 2015;16:281–92.
57. Zschaek S, Simon M, Löck S, et al. PRONTOX - proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung carcinomas (NSCLC): study protocol for a randomised controlled trial. *Trials* 2016;17:1–7.
58. Chang J, Komaki R, Wen H, et al. Toxicity and patterns of failure of adaptive/ablative proton therapy for early-stage, medically inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010;80:21.
59. Hui Z, Zhang X, Starkschall G, et al. Effects of interfractional motion and anatomic changes on proton therapy dose distribution in lung cancer. *Int J Radiat Oncol Biol Phys* 2008;72:1385–95.
60. Yamamoto T, Langner U, Loo BW, Shen J, and Keall PJ. Retrospective Analysis of Artifacts in Four-Dimensional CT Images of 50 Abdominal and Thoracic Radiotherapy Patients. *Int J Radiat Oncol Biol Phys* 2008;72:1250–8.
61. Pidikiti R, Patel BC, Maynard MR, et al. Commissioning of the world's first compact pencil-beam scanning proton therapy system. *J Appl Clin Med Phys* 2018;19:94–105.
62. Landry G and Hua C ho. Current state and future applications of radiological image guidance for particle therapy. *Med Phys* 2018;45:e1086–e1095.

63. Niepel K, Kamp F, Kurz C, et al. Feasibility of 4DCBCT-based proton dose calculation: An ex vivo porcine lung phantom study. *Z Med Phys* 2019;29:249–61.
64. Heinzerling JH, Anderson JF, Papiez L, et al. Four-dimensional computed tomography scan analysis of tumor and organ motion at varying levels of abdominal compression during stereotactic treatment of lung and liver. *Int J Radiat Oncol Biol Phys* 2008;70:1571–8.
65. Gorgisyan J, Munck af Rosenschold P, Perrin R, et al. Feasibility of pencil beam scanned intensity modulated proton therapy in breath-hold for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017;99:1121–8.
66. Dueck J, Knopf AC, Lomax A, et al. Robustness of the Voluntary Breath-Hold Approach for the Treatment of Peripheral Lung Tumors Using Hypofractionated Pencil Beam Scanning Proton Therapy. *Int J Radiat Oncol Biol Phys* 2015;53:822–34.
67. Sarrut D, Boldea V, Ayadi M, et al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:594–607.
68. 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;94:478–92.
69. Kaza E, Dunlop A, Panek R, et al. Lung volume reproducibility under ABC control and self-sustained breath-holding. *J Appl Clin Med Phys* 2017;18:154–62.
70. Kanehira T, Matsuura T, Takao S, et al. Impact of real-time image gating on spot scanning proton therapy for lung tumors: a simulation study. *Int J Radiat Oncol Biol Phys* 2017;97:173–81.
71. Shimizu S, Miyamoto N, Matsuura T, et al. A proton beam therapy system dedicated to spot-scanning increases accuracy with moving tumors by real-time imaging and gating and reduces equipment size. *PLoS ONE* 2014;9:3–9.
72. Gelover E, Deisher AJ, Herman MG, Johnson JE, Kruse JJ, and Tryggestad EJ. Clinical implementation of respiratory-gated spot-scanning proton therapy: An efficiency analysis of active motion management. *J Appl Clin Med Phys* 2019;20:99–108.
73. Schätti A, Zakova M, Meer D, and Lomax AJ. The effectiveness of combined gating and re-scanning for treating mobile targets with proton spot scanning. An experimental and simulation-based investigation. *Phys Med Biol* 2014;59:3813–28.

74. Yamada T, Miyamoto N, Matsuura T, et al. Optimization and evaluation of multiple gating beam delivery in a synchrotron-based proton beam scanning system using a real-time imaging technique. *Phys Med* 2016;32:932–7.
75. Hiraoka M, Mizowaki T, Matsuo Y, Nakamura M, and Verellen D. The gimbaled-head radiotherapy system: Rise and downfall of a dedicated system for dynamic tumor tracking with real-time monitoring and dynamic WaveArc. *Radiother Oncol* 2020.
76. Booth J, Caillet V, Briggs A, et al. MLC tracking for lung SABR is feasible, efficient and delivers high-precision target dose and lower normal tissue dose. *Radiother Oncol* 2020.
77. Hoogeman M, Prévost JB, Nuytens J, Pöll J, Levendag P, and Heijmen B. Clinical Accuracy of the Respiratory Tumor Tracking System of the CyberKnife: Assessment by Analysis of Log Files. *Int J Radiat Oncol Biol Phys* 2009;74:297–303.
78. van der Voort van Zyp NC, Prévost JB, Hoogeman MS, et al. Stereotactic radiotherapy with real-time tumor tracking for non-small cell lung cancer: Clinical outcome. *Radiother Oncol* 2009;91:296–300.
79. Fattori G, Zhang Y, Meer D, Weber DC, Lomax AJ, and Safai S. The potential of Gantry beamline large momentum acceptance for real time tumour tracking in pencil beam scanning proton therapy. *Sci Rep* 2020;10:1–13.
80. Water S van de, Kreuger R, Zenklusen S, Hug E, and Lomax A. Tumour tracking with scanned proton beams: assessing the accuracy and practicalities. *Phys Med Biol* 2009;54:6549–63.
81. Vemprala S, Saripalli S, Vargas C, Bues M, Hu Y, and Shen J. Real-Time Tumor Tracking for Pencil Beam Scanning Proton Therapy. *IEEE Int Conf Intell Rob Sys* 2018:4434–40.
82. Zhang Y, Knopf AC, Tanner C, and Lomax A. Online image guided tumour tracking with scanned proton beams: a comprehensive simulation study. *Phys Med Biol* 2014;59:7793–817.
83. Richter D, Graeff C, Jäkel O, Combs SE, Durante M, and Bert C. Residual motion mitigation in scanned carbon ion beam therapy of liver tumors using enlarged pencil beam overlap. *Radiother Oncol* 2014;113:290–5.
84. Furukawa T, Inaniwa T, Sato S, et al. Moving target irradiation with fast rescanning and gating in particle therapy. *Med Phys* 2010;37:4874–9.

85. Zhang Y, Knopf AC, Weber DC, and Lomax AJ. Improving 4D plan quality for PBS-based liver tumour treatments by combining online image guided beam gating with rescanning. *Phys Med Biol* 2015;60:8141–59.
86. Knopf AC, Hong TS, and Lomax A. Scanned proton radiotherapy for mobile targets - the effectiveness of re-scanning in the context of different treatment planning approaches and for different motion characteristics. *Phys Med Biol* 2011;56:7257–71.
87. Bernatowicz K, Lomax AJ, and Knopf A. Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients. *Phys Med Biol* 2013;58:7905–20.
88. Zenklusen SM, Pedroni E, and Meer D. A study on repainting strategies for treating moderately moving targets with proton pencil beam scanning at the new gantry 2 at PSI. *Phys Med Biol* 2010;55:5103–21.
89. Grassberger C, Dowdell S, Sharp G, and Paganetti H. Motion mitigation for lung cancer patients treated with active scanning proton therapy. *Med Phys* 2015;42:2462–9.
90. Graeff C. Motion mitigation in scanned ion beam therapy through 4D-optimization. *Physica Medica* 2014;30:570–7.
91. Liu W, Schild SE, Chang JY, et al. Exploratory study of 4D versus 3D robust optimization in intensity-modulated proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2017;95:523–33.
92. Ge S, Wang X, Liao Z, et al. Potential for improvements in robustness and optimality of intensity-modulated proton therapy for lung cancer with 4-dimensional robust optimization. *Cancers* 2019;11:35.
93. Yu J, Zhang X, Liao L, et al. Motion-robust intensity-modulated proton therapy for distal esophageal cancer. *Med Phys* 2016;43:1111–8.
94. Engwall E, Fredriksson A, and Glimelius L. 4D robust optimization including uncertainties in time structures can reduce the interplay effect in proton pencil beam scanning radiation therapy. *Med Phys* 2018;45:4020–9.
95. Korevaar EW, Habraken SJM, Scandurra D, et al. Practical robustness evaluation in radiotherapy - a photon and proton-proof alternative to PTV-based plan evaluation. *Radiother Oncol* 2019;141:267–74.
96. Fredriksson A, Forsgren A, and Hårdemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. *Med Phys* 2011;38:1672–84.

97. Liu W, Zhang X, Li Y, and Mohan R. Robust optimization of intensity modulated proton therapy. *Med Phys* 2012;39:1079–91.
98. Liu W, Frank SJ, Li X, Li Y, Zhu RX, and Mohan R. PTV-based IMPT optimization incorporating planning risk volumes vs robust optimization. *Med Phys* 2013;40:1–8.
99. Chang JY, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. *Int J Radiat Oncol Biol Phys* 2014;90:809–18.

Chapter 2

Reproducibility of the lung anatomy under active breathing coordinator control: Dosimetric consequences for scanned proton treatments

Abstract

Purpose: The treatment of moving targets with scanned proton beams is challenging. For motion mitigation, an Active Breathing Coordinator (ABC) can be used to assist breath-holding. The delivery of pencil beam scanning fields often exceeds feasible breath-hold durations, requiring high breath-hold reproducibility. We evaluated the robustness of scanned proton therapy against anatomical uncertainties when treating non-small cell lung cancer (NSCLC) patients during ABC controlled breath-hold.

Materials and methods: Four subsequent MRIs of five healthy volunteers (3 male, 2 female, age: 25-58, BMI: 19-29) were acquired under ABC controlled breath-hold during two simulated treatment fractions, providing both intrafractional and interfractional information about breath-hold reproducibility. Deformation vector fields between these MRIs were used to deform CTs of five NSCLC patients. Per patient, four or five cases with different tumor locations were modeled, simulating a total of 23 NSCLC patients. Robustly optimized (3 and 5 mm setup uncertainty respectively and 3% density perturbation) intensity-modulated proton plans (IMPT) were created and split into subplans of 20 s duration (assumed breath-hold duration). A fully fractionated treatment was recalculated on the deformed CTs. For each treatment fraction the deformed CTs representing multiple breath-hold geometries were alternated to simulate repeated ABC breath-holding during irradiation. Also a worst-case scenario was simulated by recalculating the complete treatment plan on the deformed CT scan showing the largest deviation with the first deformed CT scan, introducing a systematic error. Both the fractionated breath-hold scenario and worst-case scenario were dosimetrically evaluated.

Results: Looking at the deformation vector fields between the MRIs of the volunteers, up to 8 mm median intra- and interfraction displacements (without outliers) were found for all lung segments. The dosimetric evaluation showed a median difference in $D_{98\%}$ between the planned and breath-hold scenarios of -0.1 Gy (range: -4.1 Gy to 2.0 Gy). $D_{98\%}$ target coverage was more than 57.0 Gy for 22/23 cases. The D_{1cc} of the CTV increased for 21/23 simulations, with a median

difference of 0.9 Gy (range: -0.3 to 4.6 Gy). For 14/23 simulations the increment was beyond the allowed maximum dose of 63.0 Gy, though remained under 66.0 Gy (110% of the prescribed dose of 60.0 Gy). Organs at risk doses differed little compared to the planned doses (difference in mean doses <0.9 Gy for the heart and lungs, <1.4% difference in V_{35} [%] and V_{20} [%] to the esophagus and lung).

Conclusions: When treating under ABC controlled breath-hold, robustly optimized IMPT plans show limited dosimetric consequences due to anatomical variations between repeated ABC breathholds for most cases. Thus, the combination of robustly optimized IMPT plans and the delivery under ABC controlled breath-hold presents a safe approach for PBS lung treatments.

Introduction

Intensity modulated proton therapy (IMPT) using pencil beam scanning (PBS) is a highly conformal radiotherapy technique. Little dose is deposited after the Bragg peak, leading to improved organ at risk (OAR) sparing compared to conventional photon therapy [1, 2]. Furthermore, the intensity modulating properties of IMPT/PBS are superior to passive scattering proton therapy for modulating the dose in and around the target [1]. However, a major challenge for IMPT/PBS is the treatment of moving targets, such as in nonsmall-cell lung cancer (NSCLC) patients [3]. Breathing motion causes interplay between the timeline of the proton beam delivery and the timeline of the target motion, leading to misplacement of spots and subsequent unintended dose heterogeneities within the target volume [4, 5].

There are several techniques to mitigate breathing motion and minimize the dose degradation due to the interplay effect. Examples are rescanning, tracking, gating, and abdominal compression [5–11]. The breath-hold technique is a technique investigated initially for breast cancer patients, and later also for NSCLC patients [12, 13]. Here, the radiotherapy treatment is delivered while the patient is holding his/her breath for about 20–25 s, creating a quasi-static situation. To assist breath-holding, an Active Breathing Coordinator (ABC) (Elekta Oncology systems Ltd, Crawley, West Sussex, UK) can be used. The ABC device controls

the inspiration volume at a given threshold value and aims to produce a reproducible treatment situation. Recently, Kaza et al. investigated the reproducibility of lung volumes with ABC and found lung volume differences by 2% within and by 7% between simulated fractions [14]. Brock et al. investigated the variability in tumor position when using ABC control for photon therapy in NSCLC patients and found clinically significant tumor movements [15]. Sarrut et al. investigated the interfraction reproducibility of the lung anatomy using deformable image registration (DIR) on three repeated CT scans during ABC control [16]. They found ABC control to be effective and reproducible in 6 of 11 patients. Both Brock et al. and Sarrut et al. inspected and evaluated the local displacements, but the dosimetric consequences for IMPT/PBS therapy were not addressed. Dueck et al. investigated the robustness of single-field uniform dose plans to interfraction uncertainties between repeated voluntary breath-holds for peripheral located tumors [13]. Their conclusion was that the smaller tumors and tumors with large baseline shifts were more prone to target coverage loss.

In this study, we investigated the anatomical reproducibility of ABC controlled breath-holding in addition to the work performed by Kaza et al. for both intra- and interfraction uncertainties. This is possible due to the availability of subsequent breath-hold MR scans, providing information about the intrafractional reproducibility of subsequent breathholds. This information is unique and generally not accessible by conventional CT imaging due to the significant imaging dose given for each acquisition. Moreover, the dosimetric consequences of ABC breath-hold uncertainties were studied. We evaluated robustly optimized IMPT plans which present the state-of-the-art for proton treatments of locally advanced NSCLC patients. The aim of this study was to determine whether the combination of robustly optimized IMPT plans and the delivery under ABC controlled breath-hold presents a safe approach for PBS lung treatments.

Materials and methods

Data acquisition

Three-dimensional T1-weighted MRIs were collected from five representative consented volunteers (3 males, 2 females, age: 25-58 yr, height: 1.65-1.93 m, BMI: 19-29) at the Institute of Cancer Research in London. As described by Kaza et al., a volumetric interpolated breath-hold examination (VIBE) sequence was used (TR 4 ms, TE 0.93 ms, field-of-view 299*399 mm², acquisition matrix 324*576 interpolated, flip angle 8°, acceleration factor GRAPPA3) [14]. The image voxel size was 0.7 x 0.7 x 3.0 mm³. MR imaging was performed under ABC controlled breath-holding, at the 75% threshold of the prior determined maximum deep inspiration volume. The ABC apparatus was modified to be MR-compatible, as described by Kaza et al. [17]. Only one breath-hold was required to image the complete lung volume, with a breath-hold duration of either 22.5 or 25.0 s, according to the number of partitions required. To simulate the fractionated treatment, image acquisition was repeated after 1-4 weeks. During each session, four subsequent MRIs were acquired under ABC controlled breath-hold, resulting in eight MRIs per volunteer providing both intra- and interfraction information about the lung anatomy reproducibility. Imaging was performed using a modified extended wing board for radiotherapy (Oncology Systems Limited, Shropshire, UK).

Deformable image registration

Between the acquired MRIs for each volunteer, a global rigid image registration was applied to account for setup uncertainties. Next, DIR was performed using Mirada's multimodal algorithm RTx v1.6 (Mirada Medical, Oxford, UK). It was done locally on the lung volumes, with a grid resolution of 3.5 x 2.0 x 3.0 mm³. The first MRI of the first simulated fraction was designated as the planning MRI. By deforming the planning MRI to the three other MRIs of the same fraction and comparing the resulting deformation vector fields (DVF) DVF_A1A2, DVF_A1A3, and DVF_A1A4, the intrafraction reproducibility of the lung anatomy during breath-hold was investigated. The interfraction anatomical reproducibility was inves-

tigated by comparing the DVF_A1B1, DVF_A1B2, DVF_A1B3, and DVF_A1B4 resulting from deforming the planning MRI of the first simulated fraction.

Displacement magnitudes

Magnitude vectors in 3D were calculated from the DVFs and combined for all seven DVFs in each of the five volunteers using Matlab (v8.3, MathWorks, Natick, MA, USA). To analyze the anatomical displacements on a local level, the lung volumes were divided into seven segments: an apical region, a right/left upper and lower mid region, and a right/left caudal region (Fig. 1b).

Deformed CT scans

To generate IMPT/PBS treatment plans and to assess the dosimetric impact of the breath-hold reproducibility, we generated synthetic CT scans from the MRI data set using the following method:

- Breath-hold CTs of five NSCLC patients (2 males, 3 females, 54-69 yr.) were selected (Table 1). They were matched to respective volunteers based on a visual anatomical match of the lung volumes (Fig. 2).
- With Transformix (see elastix toolbox [18]) the CTs were transformed using the DVFs from the matched volunteer.

This was performed for all seven DVFs (DVF_A1A2, DVF_A1A3, DVF_A1A4, DVF_A1B1, DVF_A1B2, DVF_A1B3, DVF_A1B4). This resulted in a set of seven deformed CTs (A2, A3, A4, B1, B2, B3, B4) with different breath-hold geometries per patient.

Table 1. Patient and tumor characteristics

Patient number	Gender	Age	Tumor volume	TNM stage	Original tumor location
1	male	69	38.5 cm ³	T3N2M0	Left upper lobe
2	male	67	13.5 cm ³	T4N0M0	Right upper lobe
3	female	56	6 cm ³	T3N2M0	Right middle lobe
4	female	58	22.6 cm ³	T3N3M0	Left lower lobe
5	female	54	31.6 cm ³	T3N3M0	Left upper/lower lobe

Figure 1. (a) Range of intrafractional (upper boxplots) and interfractional displacements (lower boxplots) for the five volunteers. The middle line in the boxes indicates the median and the bottom and top edges of the boxes the 25th and 75th percentiles. Up to the whiskers the most extreme data points not considered outliers are shown. (b) Coronal view of an MR scan overlaid with the deformation vector fields of a deformable image registration between two MRIs for one volunteer. The lung contour was used to guide the deformable registration algorithm. The seven segments that overlap with the lung contour represent the local regions for which the magnitudes of displacement were analyzed.

Lung tumor modeling

For each patient, we simulated the original tumor configuration plus three other tumor locations. This is to assess the dosimetric impact of the found displacements between breath-holds for different tumor locations. Involved lymph nodes located in the mediastinum were not included in this simulation, as only the lung anatomy reproducibility is investigated. When the original tumor location was not close to the heart, a fourth simulated tumor location was added. The mean gross target volume (GTV) was 22.4 cm^3 (range: $6.0\text{--}38.5 \text{ cm}^3$). The GTVs were delineated on the original breath-hold CTs in RayStation (v.4.99, RaySearch Laboratories Ltd., Stockholm, Sweden). For each simulation the original GTV contour was translated and given a density of 1.05 g/cm^3 to simulate tumor tissue. The simulated locations included the upper and lower left lung lobes and the middle/upper and lower lobes of the right lung [Figs. 2(f)–2(i)]. GTVs were expanded by 5 mm to create the clinical target volumes (CTV). The CTVs were then deformably warped from the CTs toward the deformed CTs.

Figure 2. (a)-(e) Fused coronal views of the five patient/volunteer matches. 3D views of simulated tumor locations for patient number one, including the original tumor location in the left upper lobe (f), left lower lobe (g), right middle lobe (h), and right lower lobe (i).

Treatment planning

For each of the original and simulated locations (23 cases in total) intensity-modulated proton therapy plans were created (RayStation v4.99, RaySearch Laboratories Ltd., Stockholm, Sweden). The treatment was given in 25 fractions of 2.4 Gy in 5 weeks to a dose of 60.0 Gy, according to institutional policy. The treatment delivery system was the Proteus PLUS proton system (IBA, Belgium), including a scanning spot size of 6.5 mm at 70 MeV and 3 mm at 230 MeV (1 sigma). A two-beam or three-beam approach was applied depending on the

complexity of the case. Beam angles in posterior-anterior (PA), posterior-oblique (PO), and lateral (L or R) directions were selected for simulated tumors located posteriorly. Anterior-posterior (AP), anterior-oblique (AO), and lateral (L or R) directions were selected for the anteriorly located tumors. For two-beam configurations only the PA or AP beams and lateral beams were used. To account for setup errors and range uncertainties, minimax robust optimization was applied [19–22]. Two treatment plans were created for every case to investigate the effect of ABC breath-holding uncertainties to treatment plans with different target dose conformities. For the first treatment plan a robustness to 3.0 mm shifts in all directions was aimed at in addition to 3% range uncertainties. A robustness to 5.0 mm shifts in all directions was the aim for the second treatment plan together with 3% range uncertainties. Optimization settings included a set of objectives for the CTV (min dose 59.5 Gy [robust], uniform dose in CTV 60.0 Gy [robust]), and a constraint for the maximum dose (63.0 Gy) within the body. Also, objectives were used for the heart (mean dose, $V_{5\text{Gy}}$ [%]), lungs (mean dose and $V_{20\text{Gy}}$ [%]), esophagus ($V_{35\text{Gy}}$ [%] or $D_{1\text{cc}}$ [Gy]), and spinal cord ($D_{0.1\text{cc}}$ [Gy]) to reduce any dose as much as possible, without compromising the robustness of the treatment plan. To stimulate conformal treatment plans, two dose fall-offs were used. The first dose fall-off was intended to create a steep high dose gradient (60.0-30.0 Gy) around the CTV and the second dose fall-off was used to create a gradient from 60.0 to 0.0 Gy dose. A uniform dose grid size was used of 3.0 mm, and a minimum spot weight of 0.011 MU/fraction. During optimization, a constant RBE correction of 1.1 was applied [23]. After optimization, the robustness was evaluated with an in-house developed script, applying 14 different setup scenarios accounting for either 3 or 5 mm shifts and 3% range uncertainties. In total, 28 scenarios were evaluated from which a voxel-wise minimum dose distribution was calculated [20, 24]. The minimum dose required to be given to 98% of the CTV ($D_{98\%}$) was 57.0 Gy for the voxel-wise minimum dose.

Simulation of ABC controlled treatment delivery

To simulate a treatment delivery during breath-hold, each plan was split into sub-plans with delivery duration of 20 s (assumed breath-hold duration). The number

of simulated breath-holds varied per case. An overview of required breath-holds is shown in Table 2.

Next, the subplans were recalculated on the deformed CTs to simulate the dosimetric consequences of using ABC. The full fractionated treatment course was simulated rotating between all available deformed CT scans, starting with the original CT for the first breath-hold, followed by CT-A2, then CT-A3 and CT-A4. For fractions 1-12 only the deformed CTs with intrafraction uncertainties were considered. For fractions 13-25 deformed CTs with interfraction uncertainties were included, simulating an increase in uncertainties with progressing treatment duration. A schematic overview of the subplan recalculation for one representative patient case is given in Table 3. Dose distributions of the subplans recalculated at the deformed CT scans were mapped to the planning CTs and summed for dosimetric evaluation.

Table 2. The number of breath-holds (20 s. duration) required to deliver one treatment fraction per case and patient for 3 mm and 5 mm setup robustness.

	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5
	Number of breath-holds									
	3 mm setup robustness					5 mm setup robustness				
Left upper lobe	5	7	4	7	4	5	7	4	7	4
Left lower lobe	-	4	6	6	7	-	4	5	6	7
Right upper lobe	6	6	5	-	4	8	6	6	-	4
Right middle lobe	6	7	4	4	6	8	7	4	4	7
Right lower lobe	6	4	3	7	9	6	6	3	7	8

Table 3. Overview of the dose recalculation (fully fractionated treatment) for the breath-hold delivery scenario for one sample case with a three-beam configuration. Each beam requires two breath-holds to deliver.

		Beam 1	Beam 2	Beam 3
Fraction 1-12	breath-hold 1	CT A2	CT A4	CT A3
	breath-hold 2	CT A3	CT A2	CT A4
Fraction 13-25	breath-hold 1	CT B1	CT B3	CT B1
	breath-hold 2	CT B2	CT B4	CT B2

Worst-case scenario simulation

In addition to the described breath-hold scenario, a worst-case scenario was simulated for all treatment plans. The whole treatment plan was recalculated on one deformed CT scan deviating the most from the planning CT scan (CT-B4). This way a systematic error was introduced for all fractions.

Dosimetric evaluation

Several dosimetric parameters were compared between the original treatment and the recalculated plans, according to our institutional policy. Regions of interest that were evaluated included the CTV, heart, lungs (minus GTV), esophagus, and spinal cord. The $D_{98\%}$ (Gy) and D_{1cc} (Gy) of the CTV were evaluated. For the heart and lungs, the mean doses were analyzed. Furthermore, the volume receiving 35 Gy and 20 Gy (V_{35Gy} [%], V_{20Gy} [%]) to, respectively, the esophagus and lungs was evaluated as well as the dose to 0.1cc ($D_{0.1cc}$ [Gy]) of the spinal cord volume.

Results

Magnitudes of displacements

Fig. 1(b) shows the coronal view of a deformable image registration between two MRIs for one volunteer. The displacement magnitudes for all volunteers are shown in Fig. 1(a). The median intrafraction displacement was 1.3 mm and ranged for the segments between 0.8 mm and 1.6 mm. For the midregions, the right lung showed larger intrafraction displacements compared to the left lung (median increased with 0.1-0.3 mm). Interfraction displacements were larger than intrafraction displacements for all regions (median 1.6 mm [range: 1.2-1.9 mm]). Most displacements (75%) remained below 4.0 mm. Maximum displacements (without outliers) reached 5.7 mm intrafractionally and did not exceed 8.0 mm interfractionally. The anatomical reproducibility decreased from the apical regions (maximum displacements <3.0 mm) toward the caudal regions (<8.0 mm maximum displacements).

Dosimetric evaluation of target coverage

Fig. 3 shows the $D_{98\%}$ of the CTV for the different simulations and combined for all patients. All nominal plans passed the above described robustness evaluation and were clinically approved based on this evaluation. For the 3 mm setup margin, 22/23 simulations of the breath-hold scenario achieved the minimally clinically required dose of 57.0 Gy, whereas 18/23 simulations of the worst-case scenario did. One simulation (pt. 4: right lower lobe) of the breath-hold scenario showed a $D_{98\%}$ of 60.6 Gy, beyond the described dose. For the 5 mm setup margin, the minimum dose of 57.0 Gy that is considered clinically acceptable was achieved for 22/23 simulated breath-hold scenarios and for 21/23 simulated worst-case scenarios. Two simulations (pt. 2: right middle lobe, pt. 3: right lower lobe) showed an increase in $D_{98\%}$ extending beyond the prescribed dose of 60.0 Gy (61.5 Gy and 60.6 Gy respectively) for the breath-hold scenario. Table 4 shows the differences in $D_{98\%}$ between the planned doses and breath-hold or worst-case scenario, for both 3 mm and 5 mm setup robustness settings. For the breath-hold scenario, the difference in $D_{98\%}$ was larger for the middle and lower lobe simulations (median: -0.6 Gy [range: -5.4 to 1.0 Gy]) compared to the upper lobe simulations (median: -0.1 Gy [range: -1.0 to 0.3 Gy]). Also for the 5 mm setup robustness setting, the difference between breath-hold scenario and planned doses was larger for the middle and lower lobe simulations (median: -0.2 Gy [range: -4.1 to 2.0 Gy]) compared to the upper lobe simulations (median: -0.1 Gy [range: -0.6 to 0.3 Gy]). Fig. 4 shows the results of the D_{1cc} to the CTV. For the 3 mm setup robustness setting, the D_{1cc} increased for 19/23 breath-hold scenario and 21/23 worst-case scenario simulations. 18 of 23 simulations were beyond the maximum dose of 63.0 Gy for the breath-hold scenario and 15/23 worst-case simulations exceeded this threshold. Evaluating the results using the 5 mm setup robustness setting, D_{1cc} increased for 21/23 simulations for both breath-hold and worst-case scenarios. For 14/23 breath-hold scenario and 8/23 worst-case scenario simulations the increment was beyond the allowed maximum dose of 63.0 Gy. Table 4 shows the differences in D_{1cc} for both robustness settings and the breath-hold and worst-case scenario compared to the planned doses. For the breath-hold scenario and 3 mm setup robustness setting, the median difference

in D_{1cc} was smaller for the upper lobe simulations (0.2 Gy [range: -0.4 to 2.2 Gy]) compared to the middle and lower lobe simulations (0.7 Gy [range: -0.5 to 6.1 Gy]). Also for the 5 mm setup robustness setting, the median difference in D_{1cc} was smaller for the upper lobe simulations (0.5 Gy [range: -0.3 to 1.7 Gy]) compared to the middle and lower lobe simulations (1.1 Gy [range: 0.0-4.6 Gy]).

Dosimetric evaluation of organs at risk

Table 4 contains the differences in dose for the heart and lungs for the breath-hold and worst-case scenarios compared to the planned doses. Also the volume differences in the esophagus receiving 35.0 Gy and the lungs receiving 20.0 Gy are shown, when comparing the results of the breath-hold scenario and worst-case scenario with the planned doses. Both the 3 mm setup and 5 mm setup robustness settings results are shown.

Figure 3. The dose at 98% of the CTV for each simulation and all patients. The tolerance threshold (dotted line) was set to 57.0 Gy of minimum target coverage.

Table 4. Dosimetric results for CTV and organs at risk shown as differences (mean [range]) between the breath-hold scenario or worst-case scenario and the planned dose/volume parameters. Shown for both 3 mm and 5 mm setup robustness settings.

	Planned Median (range)		Planned - Breath-hold scenario Median (range)		Planned - Worst-case scenario Median (range)	
	3 mm setup robustness	5 mm setup robustness	3 mm setup robustness	5 mm setup robustness	3 mm setup robustness	5 mm setup robustness
CTV						
D _{98%} (Gy)	59.4 (58.6-59.9)	59.0 (58.2-59.5)	-0.5 (-5.4-1.0)	-0.1 (-4.1-2.0)	0.0 (-8.0-1.3)	0.0 (-8.8-0.8)
D _{1cc} (Gy)	62.8 (61.7-62.9)	62.3 (61.1-62.9)	0.6 (-0.5-6.1)	0.9 (-0.3-4.6)	0.0 (-5.2-1.8)	0.4 (-0.2-1.7)
Heart						
D _{mean} (Gy)	1.2 (0.1-5.1)	1.4 (0.2-6.0)	0.0 (-0.1-0.3)	0.0 (-0.2-0.2)	0.0 (-0.2-0.2)	0.0 (-0.2-0.2)
Lungs						
D _{mean} (Gy)	4.0 (2.0-7.1)	4.5 (2.3-8.2)	0.0 (-0.3-0.2)	0.0 (-0.3-0.2)	0.0 (-0.3-0.5)	0.0 (-0.9-0.5)
V _{20Gy} (%)	7.8 (3.9-13.7)	8.8 (4.4-16.7)	0.0 (-0.5-0.3)	0.0 (-0.6-0.3)	0.0 (-1.4-0.6)	0.0 (-1.6-1.2)
Esophagus						
V _{35Gy} (%)	0.0 (0.0-12.4)	0.0 (0.0-14.3)	0.0 (-0.1-0.3)	0.0 (-0.4-0.5)	0.0(-0.9-0.9)	0.0 (-0.4-1.1)
Spinal cord						
D _{0.1cc} (Gy)	0.1 (0.1-15.3)	0.1 (0.0-22.0)	0.0 (-0.1-1.0)	0.0 (-0.4-1.4)	0.0 (-1.9-1.6)	0.0 (-3.2-7.5)

CTV, clinical target volume; D_{98%}, dose given to 98% of volume; D_{1cc}, dose given to 1 cc of volume; D_{mean}, mean dose; V₂₀, volume receiving 20 Gy; V₃₅, volume receiving 35 Gy; D_{0.1cc}, dose given to 0.1cc of volume.

Figure 4. The dose to 1 cc of the CTV for each simulation and all patients. The tolerance threshold of the maximum dose (dotted line) was set to 63.0 Gy.

Discussion

In this study, we investigated the intra- and interfractional anatomical reproducibility of ABC controlled breath-holds. Moreover, we investigated the dosimetric consequences of ABC breath-hold uncertainties during IMPT/PBS proton treatment in a representative population (23 simulated NSCLC patients). Up to 2 mm median intra- and interfraction displacements were found for all lung regions. The maximum displacements increased from the apical regions (~3 mm) toward the caudal regions (~8 mm). Looking at the possible dosimetric impact of the found displacements for 5 mm setup robustness, the evaluation of $D_{98\%}$ showed for only one breath-hold scenario simulation a clinical relevant decrease in target coverage ($D_{98\%} = 55.0$ Gy). Two worst-case scenario simulations showed a clinical relevant decrease in target coverage ($D_{98\%} = 50.0$ Gy and 56.8 Gy). Two simulations of the breath-hold scenario showed a relevant increase in the target dose ($D_{98\%} = 61.5$ Gy and 60.6 Gy, $D_{1cc} = 65.2$ Gy and 64.5 Gy respectively). Twelve more simulations showed a relevant increase in D_{1cc} alone (63.0 - 65.5 Gy) compared to eight increased D_{1cc} (63.2 - 64.5 Gy) of the worst-case scenario simulations. However, this increase was still below a maximum of 110% of the prescribed dose. Evaluating these results with the ones observed for the 3 mm setup robustness, the number of decreased $D_{98\%}$ target coverage remained the same for the breath-hold scenario simulations. It increased from two to four simulations for the worst-case scenario ($D_{98\%} = 48.9$ - 56.2 Gy). Only one simulation showed a relevant increase in both D_{1cc} and $D_{98\%}$. The number of simulations with increased D_{1cc} was more compared to the 5 mm robustness setting (17/23 breath-hold scenario simulations and 15/23 worst-case simulations). We observed that ABC controlled breath-holding can affect the target coverage by inducing hotspots reducing the target dose homogeneity. This was seen for more simulations using the 3 mm setup robustness setting. Still, the differences between the 3 mm robustness and 5 mm setup robustness setting were relatively small and for most simulations the increased dose heterogeneity stayed within clinical acceptable limits. Moreover, dose differences in the organs at risk were minimal for all scenarios and simulations.

Brock et al. investigated the variability in tumor position and concluded that

the intrafraction uncertainties were small (1.5-1.7 mm in all directions). Our finding of a small median displacement for all regions (1.7 mm) confirmed these previous results. For interfraction changes of the lung anatomy, Sarrut et al. found a median displacement of 2.6 mm for eight patients and Brock et al. measured mean displacements of less than 5.1 mm (superior-inferior) [15, 16]. We only observed a small increase in median displacements for interfractional changes that remained under 2.0 mm (0.2-0.6 mm median increase). Dueck et al. investigated the robustness of voluntary breath-holding for PBS and concluded that small tumors and large baseline shifts are more prone to target coverage loss [13]. In the current study, we added the effect of intrafraction motion uncertainties and we especially evaluated uncertainties induced by ABC controlled breath-holding. Furthermore, in contrast with the single-field uniform dose optimized treatment plans created in the study by Dueck et al. we investigated the dosimetric effect for robustly optimized IMPT treatment plans, which are considered as state-of-the-art for PBS proton therapy and will be the treatment technique used at our facility.

To calculate the displacements between the breath-hold MRIs, deformable image registration was used. As we applied the multimodal algorithm locally on the lungs, sliding boundaries were not considered. Most of the DIR-involved uncertainties are considered to be around 2.0 mm, which is also the median of the displacements found [25]. However, locally we found much larger displacements up to 7.0 mm, which is beyond the range of errors associated with DIR.

Our breath-hold data were derived from healthy volunteers. We expect that healthy volunteers can hold the breath-hold more easily than patients. However, ABC controlled breath-hold as motion mitigation technique will only be applied to patients who are able to at least hold their breath for 20 s. We therefore assume the volunteer data as representative also for the clinical situation.

A limitation of the assessment of anatomical reproducibility based on DVFs obtained from healthy volunteers is that individual tumor movements cannot be considered. Furthermore, involved lymph nodes of the original cases were not included as only the lung anatomy reproducibility is investigated, where the

lymph nodes are located in the mediastinum.

In this study we investigated the reproducibility of ABC breath-holding, where there might be other breath-holding uncertainties that negatively affect the planned dose distributions. One such phenomenon is breath-hold drifting. Especially when reproducing a number of breath-holds this drifting can occur. A limitation of this study is that we did not investigate this effect with the limited number of breath-holds (four per session), however this would be interesting to investigate for future work. For clinical implementation, image surface scanning could provide a way to monitor the stability of the breath-hold (e.g. drifting, slowly exhaling), by imaging the chest surface. This could be in addition to the ABC breath-hold device, that reproduces the same amount of air that is inhaled.

With our data set we can only approximate a realistic treatment delivery under ABC controlled breath-hold. A limited number of four intrafraction ABC breath-hold variations and four interfraction ABC breath-hold variations for only two simulated fractions were available. A complete course of treatment will generally consist of 25 fractions and the delivery of a single fraction took according to our simulations between three and nine breath-holds. However, this is the first study evaluating dosimetrically both intra- and interfraction uncertainties. The found uncertainties using four breath-holds and two separate sessions have proven to show only limited dosimetric differences in two different robustness settings and two different scenarios. We can only speculate about the increased dosimetric differences when more than four breath-holds would have been evaluated per session. By using our data iteratively and in an alternating way we were confident of reflecting the realistic situation with adequate accuracy.

The errors of setup and range during irradiation and the breath-hold reproducibility were evaluated separately, and we did not evaluate the robustness of the treatment plans to the combined effects of residual setup errors and range errors. However, especially 5 mm setup robustness is quite generous considering a semi-static treatment situation using ABC breath-holding after the normal setup positioning using CBCT imaging. We expect that for breath-holding

this added effect of the combination of the residual setup and range error and breath-holding will be limited.

Finally, the matching of volunteers MRIs with CTs of patients may be improved by use of CT images during repeated breath-holds to directly create treatment plans and address the dosimetric differences. However, CT image acquisition during eight breath-holds, of which four repeated breath-holds per session, is not justifiable for imaging dose reasons. Thus, comprehensive information about repeated breath-holds could only be obtained with MRI. NSCLC patients would have possibly provided a better resemblance of ABC breath-hold uncertainties. This is because there might be differences in compliance between healthy and nonhealthy lung tissue, affecting the reproducibility of breath-hold. However, an addition of eight times MR imaging to the already extensive treatment and imaging schedule of actual patients is considered too much of a time burden.

A prerequisite for small dosimetrical differences between the original and the breath-hold recalculated plans is the applied robust optimization settings (5 mm or 3 mm shifts and 3% range uncertainties). With especially the 5 mm setup setting, the majority of the ABC breath-hold uncertainties were accounted for in our study. The question arises what robustness optimization setting would be optimal. A higher robustness inevitably compromises healthy tissue, but ensures adequate target coverage. Where smaller setup robustness settings increase the dose inhomogeneity gradually as observed for the 3 mm setup setting. As future work, we plan to find an optimal cut-off point between high dose region conformity and robustness of the treatment plan, especially when using ABC controlled breath-hold. We will assess this cut-off based on risk of compromising target coverage. Patients at higher risk possibly need larger margins; however, patients at lower risk should be planned with smaller margins aiming for more conformity. Moreover, for clinical implementation repeat breath-hold imaging is recommended to assess the patient specific breath-hold reproducibility. This to assure that any extremes in reproducibility can be detected and accounted for during the treatment planning.

Conclusion

The use of ABC for NSCLC patients can be considered safely for IMPT/PBS proton therapy when robust optimization is used during treatment planning. This study indicates that ABC controlled breath-hold reproducibility uncertainties will not compromise robustly optimized IMPT/PBS plans.

References

1. Zhang X, Li Y, Xiaoning P, 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. *Int J Radiat Oncol Biol Phys* 2010;77:357–66.
2. Berman AT, Teo BKK, Dolney D, et al. An in-silico comparison of proton beam and IMRT for postoperative radiotherapy in completely resected stage IIIA non-small cell lung cancer. *Rad Onc* 2013;8:1–11.
3. Lomax A. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. *Phys Med Biol* 2008;53:1043–56.
4. Bert C, Grözinger SO, and Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Phys Med Biol* 2008;53:2253–65.
5. Lomax A. SFUD, IMPT and plan robustness. In: *Particle radiotherapy*. Ed. by Rath A and Sahoo N. Springer, New Delhi, 2016:169–94.
6. Knopf AC, Hong TS, and Lomax A. Scanned proton radiotherapy for mobile targets - the effectiveness of re-scanning in the context of different treatment planning approaches and for different motion characteristics. *Phys Med Biol* 2011;56:7257–71.
7. Grassberger C, Dowdell S, Sharp G, and Paganetti H. Motion mitigation for lung cancer patients treated with active scanning proton therapy. *Med Phys* 2015;42:2462–9.
8. Zhang Y, Knopf AC, Tanner C, and Lomax A. Online image guided tumour tracking with scanned proton beams: a comprehensive simulation study. *Phys Med Biol* 2014;59:7793–817.

9. Water S van de, Kreuger R, Zenklusen S, Hug E, and Lomax A. Tumour tracking with scanned proton beams: assessing the accuracy and practicalities. *Phys Med Biol* 2009;54:6549–63.
10. Zhang Y, Knopf AC, Weber DC, and Lomax AJ. Improving 4D plan quality for PBS-based liver tumour treatments by combining online image guided beam gating with rescanning. *Phys Med Biol* 2015;60:8141–59.
11. Lin L, Souris K, Kang M, et al. Evaluation of motion mitigation using abdominal compression in the clinical implementation of pencil beam scanning proton therapy of liver tumors. *Med Phys* 2017;44:703–12.
12. Remouchamps VM, Vicini FA, Sharpe MB, Kestin LL, Martinez AA, and Wong JW. Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;55:392–406.
13. Dueck J, Knopf AC, Lomax A, et al. Robustness of the Voluntary Breath-Hold Approach for the Treatment of Peripheral Lung Tumors Using Hypofractionated Pencil Beam Scanning Proton Therapy. *Int J Radiat Oncol Biol Phys* 2015;53:822–34.
14. Kaza E, Dunlop A, Panek R, et al. Lung volume reproducibility under ABC control and self-sustained breath-holding. *J Appl Clin Med Phys* 2017;18:154–62.
15. Brock J, McNair HA, Panakis N, Symonds-Taylor R, Evans PM, and Brada M. The use of the active breathing coordinator throughout radical non-small-cell lung cancer (NSCLC) radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;81:369–75.
16. Sarrut D, Boldea V, Ayadi M, et al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:594–607.
17. Kaza E, Symonds-Taylor R, Collins DJ, et al. First MRI application of an active breathing coordinator. *Phys Med Biol* 2015;60:1681–96.
18. Klein S, Staring M, Murphy K, Viergever M, and Pluim J. elastix: a toolbox for intensity-based medical image registration. *IEEE Trans Med Imaging* 2010;29:196–205.
19. Inoue T, Widder J, Dijk LV van, et al. limited impact of setup and range uncertainties, breathing motion, and interplay effects in robustly optimized intensity modulated proton therapy for stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2016;96:661–9.

20. Pflugfelder D, Wilkens J, and Oelfke U. Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy. *Phys Med Biol* 2008;53:1689–700.
21. Fredriksson A, Forsgren A, and Hårdemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. *Med Phys* 2011;38:1672–84.
22. Liu W, Zhang X, Li Y, and Mohan R. Robust optimization of intensity modulated proton therapy. *Med Phys* 2012;39:1079–91.
23. Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002;53:407–21.
24. Lomax A, Pedroni E, Rutz H, and Goitein G. The clinical potential of intensity modulated proton therapy. *Z Med Phys* 2004;14:147–52.
25. Kierkels R, Den Otter L, Korevaar E, et al. An automated, quantitative, and case-specific evaluation of deformable image registration in computed tomography images. *Phys Med Biol* 2018;63:1–10.

Chapter 3

Investigation of inter-fraction target motion variations in the context of pencil beam scanned proton therapy in non-small cell lung cancer patients

Abstract

Purpose: For locally advanced-stage non-small cell lung cancer (NSCLC), inter-fraction target motion variations during the whole time span of a fractionated treatment course are assessed in a large and representative patient cohort. The primary objective is to develop a suitable motion monitoring strategy for pencil beam scanning proton therapy (PBS-PT) treatments of NSCLC patients during free breathing.

Materials and methods: Weekly 4D computed tomography (4DCT; 41 patients) and daily 4D cone beam computed tomography (4DCBCT; 10 of 41 patients) scans were analyzed for a fully fractionated treatment course. Gross tumor volumes (GTVs) were contoured and the 3D displacement vectors of the centroid positions were compared for all scans. Furthermore, motion amplitude variations in different lung segments were statistically analyzed. The dosimetric impact of target motion variations and target motion assessment was investigated in exemplary patient cases.

Results: The median observed centroid motion was 3.4 mm (range: 0.2-12.4 mm) with an average variation of 2.2 mm (range: 0.1-8.8 mm). Ten of 32 patients (31.3%) with an initial motion <5 mm increased beyond a 5-mm motion amplitude during the treatment course. Motion observed in the 4DCBCT scans deviated on average 1.5 mm (range: 0.0-6.0 mm) from the motion observed in the 4DCTs. Larger motion variations for one example patient compromised treatment plan robustness while no dosimetric influence was seen due to motion assessment biases in another example case.

Conclusions: Target motion variations were investigated during the course of radiotherapy for NSCLC patients. Patients with initial GTV motion amplitudes of <2 mm can be assumed to be stable in motion during the treatment course. For treatments of NSCLC patients who exhibit motion amplitudes of >2 mm, 4DCBCT should be considered for motion monitoring due to substantial motion variations observed.

Introduction

Pencil beam scanning proton therapy (PBS-PT) is a conformal radiotherapy technique for treating cancer. For the treatment of locally advanced-stage non-small cell lung cancer (NSCLC), this technique can limit radiation dose to organs at risk (OARs) [1–4]. However, the high target dose conformity and the respective steep dose gradient achieved when using scanned proton therapy lead to increased sensitivity to (breathing) motion and even more to changes in the motion behavior. Additionally, the interference of the moving target and the time structure of the scanned proton beam delivery causes interplay effects that result in dose heterogeneities [5–7].

To benefit from the advantages of PBS-PT, strategies are needed for moving targets to establish treatments that are robust to these motion and interplay effects. In case of NSCLC, the effects of breathing motion can be mitigated using breath-hold techniques, rescanning, gating, tracking, abdominal compression, or a combination of the aforementioned [3, 6, 8–14]. Furthermore, 4D robust optimization has shown to increase the robustness of treatment plans against the effects of breathing motion [15–17]. The commercially available 4D robust optimization method uses the minimax robust optimization approach and includes multiple phases of a 4DCT scan as additional images during the optimization process [18, 19]. Ribeiro et al. [20] developed a comprehensive 4D robustness evaluation method (4DREM) to effectively check the combined influence of different uncertainties on PBS-PT of moving targets. Ultimately, a 4D adaptive workflow could be the solution to obtain highly conformal dose distributions not compromised by motion and other anatomical variations occurring throughout the course of fractionated treatment [21].

Patient selection is a key element in the treatment of moving targets with PBS-PT. Literature states that NSCLC patients with gross tumor volume (GTV) motion amplitudes less than 5 mm can be safely treated using rescanning only to diminish interplay effects [5, 22, 23]. However, it is not known which patients will show substantial motion variations during the course of treatment, for example, in motion amplitude. These changes might be driven by target volume shrinkage, atelecta-

sis, or the comfort of the patient. So far, only a limited number of studies have investigated these motion variations for locally advanced-stage NSCLC patients. Redmond et al. [24] evaluated the motion variation in stage III NSCLC patients for two repeated 4DCTs that were acquired during the treatment course. They did not find major changes in motion compared to the planning 4DCT. Britton et al. [25] also investigated motion variability using five to ten repeated 4DCTs for a total of eight patients with locally advanced NSCLC and found an increase in motion variation with increasing treatment weeks ($P = 0.049$). This increase indicated the need for weekly 4DCT motion monitoring. However, in this limited cohort, only two patients exhibited less than 5 mm motion at baseline.

In the study presented here, target motion variations were primarily investigated during the whole time span of a fractionated treatment course in a larger, representative population of locally advanced-stage NSCLC patients. The motion evaluation is based on repeated weekly 4DCTs as well as on daily 4DCBCTs. The main purpose of the study is to develop a suitable motion monitoring strategy for the treatment of NSCLC patients with PBS-PT during free breathing.

Materials and methods

Patient data

This study presents a retrospective inter-institutional analysis using three different datasets. All datasets included repeated 4DCT images that were acquired on a weekly basis. Additionally, one of the datasets included daily pretreatment 4DCBCT acquisitions for 10 patients. The first dataset (A) contained 21 (N)SCLC patients who gave informed consent. The patients were part of a prospective cohort pilot study (REACT, ClinicalTrials.gov Identifier NCT03024138) to evaluate the impact of inter- and intra-fraction motion variations on photon and proton dose distributions. These patients had advanced disease (stage III-IV) and received radiotherapy with curative intent in combination with chemotherapy (all but one patient) between December 2016 and November 2017. The second dataset (B) was shared following a research agreement with OncoRay and the University Proton Therapy Dresden (Faculty of Medicine and University Hospi-

tal Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany). The dataset included six stage III NSCLC patients participating in a single-center randomized clinical trial [26]. The included patients received passively scattered proton therapy. The third dataset (C) of 14 patients originates from the publicly available The Cancer Imaging Archive (TCIA) 4D Lung database [27]. This particular dataset was provided by the Virginia Commonwealth University and contained 14 patients with locally advanced NSCLC who had undergone weekly repeated 4DCT imaging [28]. This dataset was collected between 2008 and 2012 [29–31]. Accordingly, our analysis is based on a total of 41 patients. More specific patient information can be found in Table 1.

Table 1. Patient and tumor characteristics.

Factor	Number of cases	Cases (%)
Gender		
Female	16	39
Male	25	61
Tumor location		
Left upper lobe	14	34
Right upper lobe	18	44
Right middle lobe	3	7
Left lower lobe	0	0
Right lower lobe	6	15
Gross tumor volume		
<25 cm ³	16	39
25-150 cm ³	18	44
150-500 cm ³	7	17
Number of 4DCTs		
2-4	5	12
5-6	33	81
7-8	3	7

Image acquisition

Multiple weekly 4DCTs (on average five scans) were acquired for all patients. A Definition AS Open 64-RT Pro CT scanner (Siemens Medical Systems, Erlangen, Germany), a Siemens Definition AS Open CT scanner, and a Brilliance Big Bore CT scanner (Philips Medical Systems, Andover, MA) were used for acquisition of datasets A, B, and C, respectively. 4DCT scans were reconstructed with 10 breathing phases for datasets A and C (phase-based binning), and with eight phases for

dataset B (amplitude binning). To determine the respiratory phases or amplitude, an Anzai belt (Anzai Medical, Tokyo, Japan) was used for datasets A and B, and a respiratory optical surrogate signal for dataset C (Real-time Position Management [RPM] system, Varian Medical Systems, Inc.). Images were reconstructed with either 2.0 mm (datasets A and B) or 3.0 mm (dataset C) slice thickness, 1.0 mm in-plane resolution, and image size of 512×512 pixels.

Daily 4DCBCT images were acquired in addition to the weekly 4DCTs for 10 patients included in dataset A using the Elekta X-ray Volume Imager (XVI) version 5.0.2 imaging system (Elekta, Stockholm, Sweden). Each scan was acquired in 4 min with 50 degree/min gantry speed at 120 kVp, 16 mA per frame, 10 ms per frame (total 1350 frames), field-of-view of 25×25 cm, and application of a bowtie filter. Reconstruction of the 4D images was performed with 0.93 mm in-plane resolution, 2.0 mm slice thickness, and image size of 270×270 pixels.

Contour generation

All planning and repeat 4DCTs were imported into RayStation (RaySearch Laboratories, Stockholm, Sweden). The original GTVs of the primary tumor were deformably warped (ANACONDA algorithm [32]) after a rigid registration toward the 50% phases of the planning 4DCT and the repeated 4DCTs. A radiation oncologist resident (R.A.) subsequently checked the warped contours and manually corrected when necessary (e.g. because of tumor volume shrinkage). Next, the GTVs were deformably warped to the other remaining phases of the repeat 4DCTs. Those warped contours were also visually checked and manually corrected by a radiation oncologist (M.D.) when necessary.

Inter-fraction motion amplitude 4DCTs

The GTV centroid positions were determined for all phases of the available 4DCT scans. The largest distance was calculated between centroid positions for the eight (dataset B) or 10 phases (datasets A and C). This was done for three directions: superior-inferior (SI), anterior-posterior (AP), and right-left (RL). Subsequently, the total 3D displacement vector length was calculated using the three calculated distances: $\sqrt{(SI^2 + AP^2 + RL^2)}$. The resulting GTV motion amplitudes

were compared between the weekly 4DCTs for each individual patient. Additionally, target volume changes and their correlation to motion changes were evaluated. Finally, the 4DCT phases depicting the largest motion amplitude (in terms of extreme target centroid position) were determined for a subpopulation of patients. These patients had a GTV located in the lower or middle lobe (originating from datasets A and C), and thus showed more extended motion amplitudes.

Figure 1. Example of a delineated GTV (transverse view) after deformable warping and correction on a 4DCT phase and the corresponding phase on a 4DCBCT scan.

Inter-fraction motion amplitudes of daily 4DCBCTs versus weekly 4DCTs

For 10 patients originating from dataset A, daily 4DCBCTs in addition to the weekly 4DCTs were available. One patient was excluded because treatment was discontinued after 1 week. The same procedure for the motion amplitude evaluation was performed for the 4DCBCTs. The GTV contours were deformably warped from the nearest in time acquired 4DCT scan to the 4DCBCT scan, visually checked and manually corrected. This evaluation was performed for the 0% and 50% phases of the 4DCBCT scans only. A sample 4DCT and 4DCBCT from dataset A including the GTV contours are shown in Fig. 1. The GTV centroid motion of the 4DCBCTs was compared to the weekly 4DCTs in two

ways: including either two 4DCT-phases as well as the 10 phases of the 4DCT.

Location-related differences in inter-fraction motion amplitudes

The independent samples 'Kruskal-Wallis' test was performed to determine if the GTV motion found on the 4DCTs was different for different GTV locations (left upper lobe [LUL], right upper lobe [RUL], right middle lobe [RML], and the right lower lobe [RLL]). The population did not include patients with the GTV in the left lower lobe region. The GTV locations were compared for significant differences in motion amplitude. This was done pairwise to look into differences between upper and lower lobe as well as between left and right lobes. A value of $P < 0.050$ was considered significant.

Dosimetric impact of target motion and target motion assessment

To illustrate possible dosimetric consequences of interfraction motion changes, a plan robustness evaluation was performed in one example patient (#25), for whom the motion increased beyond 5.0 mm for two weekly 4DCTs. A clinical 3D robust-optimized intensity-modulated proton treatment (IMPT) plan was created. Treatment plan parameters included a prescribed dose in terms of relative biological effectiveness (RBE) of 60.0 Gy_{RBE} to the internal clinical target volume (iCTV) given in 25 fractions. A three-beam configuration was chosen (two right posterior oblique, one right lateral). Within the iCTV, a density override to muscle tissue (1.050 g/cm³) was applied during optimization. Robustness was achieved using the minimax robustness approach, with 6.0-mm setup uncertainties and 3% range uncertainties, using the average CT [18]. These were the same robustness settings as applied in the clinic. The obtained 3D-optimized plan was evaluated for its robustness on the average scans of the weekly repeat 4DCTs, applying a 2.0-mm setup uncertainty and 3% range uncertainty as explained by Ribeiro et al. [20]. Robustness results were evaluated in terms of iCTV coverage and OAR doses through the voxel-wise worst-case doses: which is the computed minimum dose per voxel obtained from 14 scenario doses. OARs voxel-wise worst-case doses were computed as the maximum dose per voxel obtained from the 14 scenario doses. Nominal doses and voxel-wise worst-case doses were evaluated

through dose volume histograms (DVHs).

Recently, 4D robust treatment plan optimization became available in RayStation. 4D robust optimization uses the minimax robust optimization approach and includes multiple phases of a 4DCT scan as additional images during the optimization process [18, 19]. This way, differences in anatomy due to breathing motion are accounted for during optimization. As a compromise between computational time and a global robustness, it needs to be decided how many and which 4DCT phases should be included in the optimization process. To assess the dosimetric impact of employing the wrong extreme phases during 4D optimization, a 4D robust-optimized treatment plan (6.0-mm setup uncertainties and 3% range uncertainties) was created for an example patient (#37), based on the 0% and 50% phase (default extreme motion phases). The treatment plan was subsequently evaluated for its robustness on the actual extreme target motion phases of the 4DCT (60% and 90% phases; 6.0-mm setup uncertainties and 3% range uncertainties) [20].

Results

Inter-fraction motion amplitudes 4DCTs

The median observed amplitude of the GTV centroid motion was 3.4 mm over all time points (range: 0.2-12.4 mm; Fig. 2). The median variation in GTV motion amplitude for individual patients was 2.2 mm (range: 0.1-8.8 mm). GTV motion in week 0 revealed an initial motion of less than 5 mm for 32 out of 41 patients (78.0%). Of these patients, 10 of 32 (31.3%) showed GTV motion >5 mm during the course of treatment for multiple weeks (median: 3 weeks, range: 14 weeks), extending up to 10.4-mm amplitude motion for the most extreme case. Only patients with initial motion of less than 2 mm (12/41 patients) remained stable in motion (<5 mm) during the course of treatment. The extreme GTV motion amplitudes were captured in the 0% and 50% 4DCT phases for 52% (SI direction), 32% (AP direction), and 44% (RL direction) of the 4DCTs, see Fig. 3. The correlation between changes in target volume and GTV motion amplitude was examined using Spearman's correlation coefficient. A significant ($P = 0.012$) correlation of 0.389

was found between the maximum volume change and maximum change in motion amplitude during the course of treatment (Fig. 4). The weekly measured target volumes are reported in the supplement (Fig. S1).

Figure 2. GTV centroid motion amplitudes for the 41 patients for the weekly 4DCTs.

Figure 3. Total count that a specific 4DCT phase contained an extreme GTV centroid position for the middle/lower lobe targets (nine patients, a total of 47 4DCTs).

Figure 4. Maximum volume changes compared to GTV maximum motion amplitude changes.

Inter-fraction motion amplitudes of daily 4DCBCTs versus weekly 4DCTs

The mean deviation between the centroid motion amplitudes of the weekly 4DCTs (all 10 phases) and daily 4DCBCTs was 1.5 mm (range: 0.0-6.0 mm; Fig. 5). When comparing the centroid motion of the 4DCBCT versus the motion amplitudes measured in the 4DCT for two phases, only two patients (4 and 7) followed the trend observed following the weekly 4DCT scans within a 1.0-mm uncertainty band (Fig. 5). The other patients were in line with the 4DCT motion for only a part of the treatment course. One exception is patient #9, who showed smaller motion (± 3 mm difference) in the 4DCBCT scans for all but one fraction.

Location-related inter-fraction motion amplitudes differences

To evaluate whether GTV motion depended on GTV location (i.e., lung lobe), pairwise comparisons were performed using the 4DCT information. Significant regional differences in motion were found (note that there were no left lower lobe patients in the study population). GTVs in the left upper lobe showed significantly larger motion compared to GTVs from the right upper lobe (mean motion

Figure 5. GTV centroid motion amplitudes from weekly 4DCTs together with the motion from daily 4DCBCTs. Patient data are presented in ascending order of motion amplitude. The highlighted colored areas show a margin of ± 1.0 mm.

4.0 mm and 2.9 mm, respectively; $P = 0.012$). Furthermore, GTV motion in the right lower lobe (mean motion = 6.5 mm) was significantly larger than the motion found in the upper lobes: 2.9 mm ($P = <0.001$) and 4.0 mm ($P = 0.020$) in the right and left lobe, respectively.

Dosimetric impact of target motion and target motion assessment

The 3D-optimized treatment plan for patient #25 was robustly evaluated through the voxel-wise worst-case doses. The iCTV coverage ($D_{98\%}$ [Gy_{RBE}]) showed a deterioration of $D_{98\%}$ for all weeks (Fig. 6). This deterioration was the largest (51.12 Gy_{RBE} and 53.94 Gy_{RBE} $D_{98\%}$) for the repeated 4DCTs in the first 2 weeks, in which the measured GTV motion increased from 2.4 mm (week 0) to 5.7 mm and 7.1 mm, respectively. The dosimetric impact of considering the "wrong" extreme motion amplitude phases during 4D robust optimization is illustrated for an example case in Fig. 7. A small decrease in $D_{98\%}$ for the voxel-wise worst-case doses was observed for the CTV ($D_{98\%}$: 57.91 Gy_{RBE} [60% phase] and 57.96 Gy_{RBE} [90% phase]).

Figure 6. Dose volume histograms (DVHs) of the iCTV (orange), heart (purple), esophagus (blue), and lungs minus GTV (green) for a 3D robust-optimized treatment plan. Depicted are the nominal doses (solid lines) and voxel-wise worst-case doses after robustness evaluation for the weekly 4DCTs (striped lines). A coronal view of the GTV location and the inter-fraction motion range is shown on the right.

Figure 7. Dose volume histograms (DVHs) of the 4D robust-optimized treatment plan using two phases (0% and 50%) for one sample patient. The nominal doses (solid lines) and voxel-wise worst-case doses on the actual extreme phases (60% and 90%) are shown (striped lines) for the CTV (orange), heart (purple), lungs minus GTV (green), and esophagus (blue). A coronal view of the GTV location is shown on the right.

Discussion

In this study the main objective was to investigate GTV motion amplitude variations of locally advanced-stage NSCLC patients during a fractionated treatment course. Approximately one third of the patients showed initially small GTV motion (<5 mm), which increased beyond 5 mm for one or multiple weeks during the course of treatment. Moreover, between individual patients, large differences were found in motion amplitude variations, ranging from "static" targets to "highly mobile" targets. Only GTVs that moved less than 2 mm prior to treatment remained at a stable low motion amplitude below 5 mm during treatment. For the patients with a GTV moving more than 2 mm, 4D motion monitoring on a daily basis will give insight in the patientspecific motion trend and can therefore prevent nonrobust treatments by adapting treatments when necessary. However, further research is required to explore the (dosimetric) implications of the observed motion amplitude variations on scanned proton treatments. Another finding was that the anatomical location of the GTV (i.e., the different lung lobes) influenced the motion extent. These findings are in line with those reported by

Seppenwoolde et al. [33], Redmond et al. [24], and Britton et al. [25], who found significantly larger motion in the lower lung lobes. Motion management for patients with lower lobe GTVs might therefore be more challenging due to the generally found larger motion amplitudes. We found a substantial volume reduction of the GTV during the course of radiotherapy (Fig. S1). Large volume reductions were also reported by Britton et al. [25], with 41.7% and 37.1% median tumor volume reduction for end-inhalation and end-exhalation phases, respectively. Brink et al. [34] reported up till 60% decrease of volume and Erridge et al. [35] reported at least 20% reduction of GTV volume for 40% of the patients. Notable volume and motion amplitude changes in our population were already observed halfway treatment. Patients with these early changes may benefit from adaptive treatment approaches. Interestingly, in our population a significant correlation was found between maximum volume changes and motion variations, indicating that larger volume reductions can lead to increased motion amplitudes (Fig. 4). Future research could investigate more thoroughly in what way volume reductions and tumor motion amplitude variations correlate and influence the target coverage independently during proton treatments. This was unfortunately beyond the scope of this study. Besides GTV volume reduction, other factors might also play an important role in motion changes, for example resolving atelectasis or pleural effusion. Patients' comfort can change over the course of treatment and this can also influence breathing motion. Baseline drifts for example have been investigated by a number of studies for patients treated with stereotactic body radiation therapy (SBRT). Takao et al. [36] examined 68 SBRT patients with real-time tumor-tracking radiation therapy (TRRT) and fiducial markers. They found >3 mm incidence of 3D vector-calculated baseline drifts for 42.1% of the population after 10 min of treatment. Malinowski et al. [37] found for 37 lung cancer patients that 13% showed >5 mm baseline drift after 20 min of treatment. The incidence and severity of the baseline drift seem to increase with the duration of treatment. Moreover, Seppenwoolde et al. [33] found motion changes between 1 and 5 mm due to hysteresis for 10 out of 21 tumors. It is important to consider these type of motion changes as well for scanned proton treatment and adjust treatment strategies accordingly. GTV motion trends extracted from weekly re-

peated 4DCTs were not reflected in the extracted motion of the 4DCBCTs at corresponding days. The large deviation for patient #9 can be explained by the fact that this patient was highly claustrophobic and heavier breathing due to anxiety was noticed during the 4DCT imaging sessions. In general, as only the 0% and 50% 4DCBCT phases were evaluated, we expected a small systematic underestimation of motion as these phases do not necessarily encompass the extreme target position. However, also deviations between extracted motions amplitudes calculated with two phases of the 4DCBCT scans versus two phases of the 4DCT scans remained (Fig. 5). The 4DCBCT acquisition time was 4 min per scan, and baseline drifts could have taken place during the acquisition compared to the 4DCT acquisitions of 1 min. This could have influenced the resulting centroid motion amplitude comparison between the two modalities. However, Takao et al. [36] found for their population that the incidence of baseline drifts rose after 3 min with only 8% of the population exhibiting drifts >3 mm after 4 min of treatment. This was also measured during the actual treatment time, after patient setup and positioning verification. We therefore can only suspect a small influence of baseline drifts on the 4DCBCT acquisitions for a part of the patient population. With respect to the observed large day-to-day motion variations in the 4DCBCTs, we recommended base treatment adaptation decisions on observed trends as proposed by Meijers et al. [21] rather than on single day recalculations.

We revealed that extreme GTV positions can occur in any 4DCT phase for NSCLC patients. In an exemplary evaluation, we did not find a substantial decrease in plan robustness when using other than the extreme motion phases for optimization. Still, our recommendation would be a careful phase selection to try capturing the full motion extent, whereas the 4D robust treatment planning time is kept reasonably limited.

In addition to currently published research, we investigated target motion variations using a comprehensive dataset that contains a substantially larger number of patients with four or more repeated 4DCTs as well as daily 4DCBCTs for a subset of patients. In contrast, previous studies analyzed only one or two repeat 4DCTs. Therefore, our study provides a deeper insight in occurring motion vari-

ations. Unfortunately, in our dataset, the GTVs are not evenly distributed within the lungs. There are notably more patients with GTVs located in the upper lobes. Nevertheless, significant differences in motion were found for the varying target locations. Quality of the 4DCT and 4DCBCT images in this study may be an issue as some 4DCT scans contained binning artifacts. Optimization of the reconstruction process may improve the quality of the images and may therefore further optimize motion evaluation. For the reconstruction of the 4DCT and 4DCBCT images, two different signals for the binning methods were used, namely an external respiratory surrogate signal using the Anzai belt (4DCT) and the internal surrogate signal using the Amsterdam Shroud method by Zijp et al. [38] (4DCBCT). The external and internal respiratory surrogate signals for image phase binning could influence the resulting image quality in a different way. Shieh et al. [39] investigated and found negligible differences in image-quality values for reconstructed 4DCBCTs between an external and internal respiratory signal surrogate. It was advised to verify these findings in a larger patient cohort. Nevertheless, we carefully conclude from these findings that differences in tumor motion estimation between 4DCT and 4DCBCT would be more apparent because of image-quality differences between the two modalities than due to inaccuracy differences between the used respiratory signals for phase binning.

There exist differences in imaging accuracy between several brands of 4DCT scanners, which can result in errors during motion estimation. This was investigated by Hurkmans et al. [40]. They investigated the range of motion error for different types of CT scanners. The type of scanner used for datasets A and B of this study would be congruent with a range of motion error of 0.3 mm. For the third dataset, the CT scanner was of another brand and for those patients the error would be around 1.0 mm. We determined that patients would remain stable during treatment when a motion of less than 2 mm was measured before start of treatment. The inaccuracy in the value of 2 mm is <1 mm.

Furthermore, the quality of the motion evaluation depended on the quality of delineations. We expect that even with a strict method of deformable warping of contours and manual checking afterward, uncertainties will remain. However,

these uncertainties will be less than the inter-observer variability for delineations [41]. Major anatomical changes (e.g, GTV shrinkage) also make it difficult to propagate GTV contours using deformable image registration algorithms alone. A thorough checking with manual adjustments was performed in this study, to cope with this issue. Furthermore, it has been shown in other studies that it is possible to combine deformable image registration algorithms for contour propagation with other (semi)automatic techniques like a watershed-cuts algorithm to improve the accuracy of the contours [42].

Conclusion

Investigation of target motion variations during the course of radiotherapy for a large group of locally advanced-stage NSCLC patients revealed that only initial GTV motion amplitudes of <2 mm seem to remain stable during the treatment course. Patients fulfilling this criterion might be less challenging for PBS-PT treatment during free breathing. For target motion amplitudes larger than 2 mm, we recommend 4DCBCT motion monitoring and base treatment adaptation decisions on observed trends.

References

1. Chang JY, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. *Int J Radiat Oncol Biol Phys* 2014;90:809–18.
2. Berman AT, Teo BKK, Dolney D, et al. An in-silico comparison of proton beam and IMRT for postoperative radiotherapy in completely resected stage IIIA non-small cell lung cancer. *Rad Onc* 2013;8:1–11.
3. Liu C, Sio TT, Deng W, et al. Small-spot intensity-modulated proton therapy and volumetric-modulated arc therapies for patients with locally advanced non-small-cell lung cancer : A dosimetric comparative study. *J Appl Clin Med Phys* 2018;19:140–8.
4. Berman A, James S, and Rengan R. Proton beam therapy for non-small cell lung cancer: current clinical evidence and future directions. *Cancers* 2015;7:1178–90.
5. Bert C, Grözinger SO, and Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. *Phys Med Biol* 2008;53:2253–65.

6. Kraus K, Heath E, and Oelfke U. Dosimetric consequences of tumour motion due to respiration for a scanned proton beam. *Phys Med Biol* 2011;56:6563–81.
7. Kang M, Huang S, Solberg TD, et al. A study of the beam-specific interplay effect in proton pencil beam scanning delivery in lung cancer. *Acta Oncol* 2017;56:531–40.
8. 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;94:478–92.
9. Gorgisyan J, Munck af Rosenschold P, Perrin R, et al. Feasibility of pencil beam scanned intensity modulated proton therapy in breath-hold for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017;99:1121–8.
10. Grassberger C, Dowdell S, Sharp G, and Paganetti H. Motion mitigation for lung cancer patients treated with active scanning proton therapy. *Med Phys* 2015;42:2462–9.
11. Furukawa T, Inaniwa T, Sato S, et al. Moving target irradiation with fast rescanning and gating in particle therapy. *Med Phys* 2010;37:4874–9.
12. Water S van de, Kreuger R, Zenklusen S, Hug E, and Lomax A. Tumour tracking with scanned proton beams: assessing the accuracy and practicalities. *Phys Med Biol* 2009;54:6549–63.
13. Lin L, Souris K, Kang M, et al. Evaluation of motion mitigation using abdominal compression in the clinical implementation of pencil beam scanning proton therapy of liver tumors. *Med Phys* 2017;44:703–12.
14. Li W, Purdie TG, Taremi M, et al. Effect of immobilization and performance status on intrafraction motion for stereotactic lung radiotherapy: analysis of 133 patients. *Int J Radiat Oncol Biol Phys* 2011;81:1568–75.
15. Cummings D, Tang S, Ichter W, et al. Four-dimensional plan optimization for the treatment of lung tumors using pencil-beam scanning proton radiotherapy. *Cureus* 2018;10:e3192.
16. Ge S, Wang X, Liao Z, et al. Potential for improvements in robustness and optimality of intensity-modulated proton therapy for lung cancer with 4-dimensional robust optimization. *Cancers* 2019;11:35.
17. Liu W, Schild SE, Chang JY, et al. Exploratory study of 4D versus 3D robust optimization in intensity-modulated proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2017;95:523–33.

18. Fredriksson A, Forsgren A, and Hårdemark B. Minimax optimization for handling range and setup uncertainties in proton therapy. *Med Phys* 2011;38:1672–84.
19. Engwall E, Fredriksson A, and Glimelius L. 4D robust optimization including uncertainties in time structures can reduce the interplay effect in proton pencil beam scanning radiation therapy. *Med Phys* 2018;45:4020–9.
20. Ribeiro C, Meijers A, Korevaar E, et al. Comprehensive 4D robustness evaluation for pencil beam scanned proton plans. *Radiother Oncol* 2019;136:185–9.
21. Meijers A, Jakobi A, Stützer K, et al. Log file-based dose reconstruction and accumulation for 4D adaptive pencil beam scanned proton therapy in a clinical treatment planning system: implementation and proof-of-concept. *Med Phys* 2019;46:1140–9.
22. Tsunashima Y. Verification of the clinical implementation of the respiratory gated beam delivery technique with synchrotron-based proton irradiation. Univ of Texas 2012.
23. Jakobi A, Perrin R, Knopf A, and Richter C. Feasibility of proton pencil beam scanning treatment of free-breathing lung cancer patients. *Acta Oncol* 2018;57:203–10.
24. Redmond KJ, Song DY, Fox JL, Zhou J, Rosenzweig CN, and Ford E. Respiratory motion changes of lung tumors over the course of radiation therapy based on respiration-correlated four-dimensional computed tomography scans. *Int J Radiat Oncol Biol Phys* 2009;75:1605–12.
25. Britton KR, Starkschall G, Tucker SL, et al. Assessment of gross tumor volume regression and motion changes during radiotherapy for non-small-cell lung cancer as measured by four-dimensional computed tomography. *Int J Radiat Oncol Biol Phys* 2007;68:1036–46.
26. Zschaek S, Simon M, Löck S, et al. PRONTOX - proton therapy to reduce acute normal tissue toxicity in locally advanced non-small-cell lung carcinomas (NSCLC): study protocol for a randomised controlled trial. *Trials* 2016;17:1–7.
27. Clark K, Vendt B, Smith K, et al. The cancer imaging archive (TCIA): maintaining and operating a public information repository. *J Digit Imaging* 2013;26:1045–57.
28. Hugo GD, Weiss E, Sleeman WC, et al. Data from 4D lung imaging of NSCLC patients. The cancer imaging archive. 2016.
29. Hugo GD, Weiss E, Sleeman WC, et al. A longitudinal four-dimensional computed tomography and cone beam computed tomography dataset for image-guided radiation therapy research in lung cancer. *Med Phys* 2017;44:762–71.

30. Roman NO, Shepherd W, Mukhopadhyay N, Hugo GD, and Weiss E. Interfractional positional variability of fiducial markers and primary tumors in locally advanced non-small-cell lung cancer during audiovisual biofeedback radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;83:1566–72.
31. Balik S, Weiss E, Jan N, et al. Evaluation of four-dimensional computed tomography to four-dimensional cone-beam computed tomography deformable image registration for lung cancer adaptive radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;86:372–9.
32. Weistrand O and Svensson S. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* 2015;42:40–53.
33. Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–34.
34. Brink C, Bernchou U, Bertelsen A, Hansen O, Schytte T, and Bentzen S. Locoregional control of non-small cell lung cancer in relation to automated early assessment of tumor regression on cone beam computed tomography. *Int J Radiat Oncol Biol Phys* 2014;89:916–23.
35. Erridge SC, Seppenwoolde Y, Muller SH, et al. Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer. *Radiother Oncol* 2003;66:75–85.
36. Takao S, Miyamoto N, Matsuura T, et al. Intrafractional baseline shift or drift of lung tumor motion during gated radiation therapy with a real-time tumor-tracking system. *Int J Radiat Oncol Biol Phys* 2016;94:172–80.
37. Malinowski K, McAvoy TJ, George R, Dietrich S, and D'Souza WD. Incidence of changes in respiration-induced tumor motion and its relationship with respiratory surrogates during individual treatment fractions. *Int J Radiat Oncol Biol Phys* 2012;82:1665–73.
38. Zijp L, Sonke J, and Herk M van. Extraction of the respiratory signal from sequential thorax cone-beam X-ray images. In: *Proceedings of the 14th ICCR*. Seoul, Korea, 2004:507–9.
39. Shieh C, Kipritidis J, O'Brien R, Kuncic Z, and Keall P. Image quality in thoracic 4D cone-beam CT: a sensitivity analysis of respiratory signal source, binning method, and reconstruction algorithm. *Med Phys* 2014;41:513.

40. Hurkmans CW, Van Lieshout M, Schuring D, et al. Quality assurance of 4D-CT scan techniques in multicenter phase III trial of surgery versus stereotactic radiotherapy (radiosurgery or surgery for operable early stage (stage 1A) non-small-cell lung cancer [ROSEL] study). *Int J Radiat Oncol Biol Phys* 2011;80:918–27.
41. Mercieca S, Belderbos JS, De Jaeger K, et al. Interobserver variability in the delineation of the primary lung cancer and lymph nodes on different four-dimensional computed tomography reconstructions. *Radiother Oncol* 2018;126:325–32.
42. Veiga C, Janssens G, Teng CL, et al. First clinical investigation of cone beam computed tomography and deformable registration for adaptive proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2016;95:549–59.

Supplementary materials

Target volumes changes

For each weekly repeat 4DCT the average volume of all phases was calculated and changes in GTV evaluated between the patients. Target volumes increased in week one to decrease again in the following weeks for 20 out of 41 patients (Figure S-1). During treatment, the average GTV reduction (either from week 0 or from week 1) was 34.3% (standard deviation [SD]: 17.3%). Halfway through treatment this reduction was on average 24.5% (SD: 16.0%).

Figure S1. Target volumes changes according to the weekly repeat 4DCTs for all patients. The volumes are shown for different lung regions as depicted in the schematic picture on the right.

Chapter 4

4D cone-beam CT reconstruction from sparse-view CBCT data for daily motion assessment in pencil beam scanned proton therapy (PBS-PT)

Abstract

Purpose: The number of pencil beam scanned proton therapy (PBS-PT) facilities equipped with cone-beam computed tomography (CBCT) imaging treating thoracic indications is constantly rising. To enable daily internal motion monitoring during PBS-PT treatments of thoracic tumors, we assess the performance of Motion-Aware RecOnstructiOn method using Spatial and Temporal Regularization (MA-ROOSTER) 4DCBCT reconstruction for sparse-view CBCT data and a realistic dataset of patients treated with proton therapy.

Materials and methods: Daily CBCT projection data for nine non-small cell lung cancer (NSCLC) patients and one SCLC patient was acquired at a proton gantry system (IBA Proteus©One). 4DCBCT images were reconstructed applying the MA-ROOSTER and the conventional phase-correlated Feldkamp-Davis-Kress (PC-FDK) method. Image quality was assessed by visual inspection, contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR) and the structural similarity index measure (SSIM). Furthermore, gross tumor volume (GTV) centroid motion amplitudes were evaluated.

Results: Image quality for the 4DCBCT reconstructions using MA-ROOSTER was superior to the PC-FDK reconstructions and close to FDK images (median CNR: 1.23 [PC-FDK], 1.98 [MA-ROOSTER], and 1.98 [FDK]; median SNR: 2.56 [PC-FDK], 4.76 [MA-ROOSTER], and 5.02 [FDK]; median SSIM: 0.18 [PC-FDK vs. FDK], 0.31 [MA-ROOSTER vs. FDK]). The improved image quality of MA-ROOSTER facilitated GTV contour warping and realistic motion monitoring for most of the reconstructions.

Conclusions: MA-ROOSTER based 4DCBCTs performed well in terms of image quality and appear to be promising for daily internal motion monitoring in PBS-PT treatments of (N)SCLC patients.

Introduction

In recent years, cone-beam computed tomography (CBCT) acquisition has become available at pencil beam scanned proton therapy (PBS-PT) facilities with

the main purpose of daily positioning and anatomy verification [1]. As PBS-PT has also been extended for an increasing number of PT facilities to treatment moving targets, daily motion monitoring in treatment position would be of added value. This would require a 4D reconstruction method where currently only 3DCBCT reconstruction software is commercially available for proton CBCT installations. In addition, to keep the imaging dose and the imaging time at the gantry as low as possible, 4DCBCT reconstruction methods are preferred that only require projection data acquired during 3DCBCT acquisition. The conventionally used phase-correlated algorithm of Feldkamp-Davis-Kress (PC-FDK) suffers from under-sampling artifacts when using a limited amount of projections [2]. One alternative is the McKinnon-Bates (MKB) or the recently published modified MBK method, which starts with a motion-blurred FDK prior image and PC-FDK data. It creates motion-encoded difference projections that are reconstructed and added to the well-sampled FDK prior image to create the higher quality 4DCBCTs [3, 4]. Other advanced 4D reconstruction methods have been reported that work well for few projection data by applying for example regularization between neighbouring reconstructed phases or using prior image constrained compressed sensing (PICCS) reconstruction [5–7]. Furthermore, motion compensated methods have proven to successfully improve the image quality [8–11]. Combinations of the different techniques have shown great potential in the last years [12–14]. Recently, the SPARE challenge was performed where several reconstruction methods for 1-min acquisitions were compared for image quality and a common framework for evaluation of reconstruction methods was built [15]. The method best performing in this challenge was the so-called Motion-Aware RecOnstructiOn method using Spatial and Temporal Regularization (MA-ROOSTER), introduced by Mory et al. [16]. For phantom data with known motion amplitudes, this method has shown to be promising to implement for scanned proton gantry systems [16]. Only one published study investigated the potential of using (sparse-view) 4DCBCTs for proton therapy treatments specifically [17]. This was done using phantom CBCT data acquired at a medical linear accelerator that was reconstructed using an iterative reconstruction method based on total variation regularization [17]. This technical

note reports on the potential of using the advanced reconstruction method MA-ROOSTER for creating 4DCBCTs from sparse-view clinical CBCT data. This was done for a representative proton therapy data set of (non-)small cell lung cancer ([N]SCLC) patients. 4DCBCT image quality was assessed as well as the internal tumor motion for its suitability for daily internal motion monitoring.

Materials and methods

Patient data

The data set consisted of nine patients with NSCLC and one patient with SCLC that were treated with PBS-PT with curative intent. For each patient, daily CBCT projection data was acquired at an IBA Proteus©One proton gantry system. The first ten fractions of CBCT projections were used in this study to show the feasibility of 4DCBCT reconstruction including daily variations in image quality. The integrated CBCT system has a source-to-axis distance of 100 cm and source-to-imager distance of 155 cm. Image acquisition settings were a field-of-view of 25 cm, 110 kVp, 25 mA and 6.4 CTDI_{weighted} (mGy). Each projection had a resolution of 1441 by 1440, with image plane pixel spacing of 0.3 mm. Acquisition was performed during a ≈ 220 -degree arc rotation, average gantry speed of 3 degrees per second and a total scan time of ≈ 1.2 minutes. Per set a total of 515 projections were acquired. The ten patients were divided in two groups for image quality assessment, based on the presence of metallic artifacts in the images. Patients #1 and #2 had a Port-a-Cath, patient #3 a trachea stoma and patient #4 a cervical fusion plate. Patient #5 had surgical clips in the breast and axillary region as this patient was treated for breast cancer. Patient #1 suffered also from high density metastatic spinal lesions. Additionally, the simulation 4D- and 3DCT scans with clinical structure sets were available. Five out of ten patients received one repeated 4DCT scan after one or two weeks of treatment, because of tumor volume shrinkage (pts. #1, #4, #9, and #10) and pleural effusion (pt. #7).

4DCBCT reconstruction

The reconstruction method of MA-ROOSTER is implemented in the Reconstruction ToolKit (RTK) library, an open source C++ software based on the

Insight Toolkit (ITK) [18]. Pre-processing was performed in the MATLAB (MathWorks, Natick, MA) based open-source collaboration software REGGUI (<https://openreggui.org/>). In REGGUI, deformable image registration (DIR) was performed (diffeomorphic morphons algorithm, developed by Janssens et al. [19]) between the simulation 4DCT phases to compute the 4D deformable vector fields (DVF). The 4D DVFs are used during temporal regularization of the MA-ROOSTER method. The complete workflow was executed on a Linux machine with Intel Xeon CPU E5-2650 processor v4 (2.4 GHz), 24 cores and 48 hyper-threads. It has 64GB DDR4 memory and two GPUs (GTX 1080 Ti) installed in parallel. An NVIDIA tesla driver (vs. 418.87.1) and CUDA (version 10.1) were utilized for fast GPU computations. The same parameter settings were applied as described by Mory et al. [16] for spatial and temporal regularization. These settings were found to be the most optimal for our patients for removing streak artifacts and at the same time prevent image blurring by over-regularization. To compare the image quality and motion monitoring performance of MA-ROOSTER reconstructions, all data was additionally reconstructed using the conventionally used PC-FDK method. PC-FDK is not considered to be equally comparable in performance, however it shows the baseline image quality when using a phase-correlated method. Also, FDK 3DCBCT images were created to show the image quality of FDK for ample projections. Both FDK and PC-FDK are available in the RTK library. Table 1 shows the other parameters and settings for MA-ROOSTER and PC-FDK. All 4DCBCTs were reconstructed in ten single respiratory phases and binned following the internal respiratory signal of the diaphragm region that was semi-automatically extracted using the Amsterdam Shroud method [20]. The size of the reconstructed images depended on the patients size and varied between 28-30 cm $\times$ 22-28 cm $\times$ 20-28 cm.

Deformable image registration for contour warping

After reconstruction, the 4DCBCT images were imported in RayStation (RaySearch Laboratories, Stockholm, Sweden), together with the 3DCBCT images, the simulation and repeat (4D)CT scans and the clinical structure sets. The simulation CTs were rigidly registered to all the 4DCBCT and 4DCT phases. Afterwards, the gross tumor volume (GTV) contours of the simulation CTs were

deformably warped to all the 4DCBCT and 4DCT phases using the ANACONDA algorithm available in RayStation [21].

Table 1: Parameters and settings of 4DCBCT reconstruction.

Parameter	MA-ROOSTER	PC-FDK
Nr. of phases	10	10
Voxel spacing (mm)	2 x 2 x 2	2 x 2 x 2
Hann windowing		0.5
Projection padding		0.1
Number of iterations	10	
Nr. of nested CG iterations	4	
Nr. of nested TV iterations	10	
Temporal regularization	0.0002	
Spatial regularization	0.00005	

CG, conjugate gradient; TV, total variation

A different DIR algorithm was chosen for contour warping compared to the DIR (diffeomorphic morphons) used during the pre-processing phase of the MA-ROOSTER reconstruction to avoid a bias towards the MA-ROOSTER reconstructions in motion estimation.

Image quality metrics

Image quality was assessed for all phases of the 4DCBCTs and the FDK images using three measures. The first two are the contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR), calculated as follows:

$$CNR = \frac{|\mu_{GTV} - \mu_{Lung}|}{\sigma_{Lung}} \quad (4.1)$$

$$SNR = \left[\frac{\mu_{Lung}}{\sigma_{Lung}} \right] \quad (4.2)$$

Where μ_{GTV} represents the average attenuation value in Hounsfield units (HU) measured in the GTV. μ_{Lung} was determined as average HU in a 2-10 mm margin surrounding the GTV. The margin was adapted to create a region of comparable volume size as the GTV. σ_{Lung} represents the standard deviations of the

HU measured in the lung margin surrounding the GTV. The contoured GTV often includes lung tissue in some extent, and therefore differs in tissue heterogeneity between patients. To determine the signal-to-noise ratio, we chose to use the surrounding and less heterogeneous lung tissue region for calculation. The third is the Structural Similarity Index Measure (SSIM), which evaluates a combination of image luminance, contrast, and structure [22]. The SSIM is available in the MATLAB environment. The comparison with SSIM was performed between each phase of the PC-FDK or MA-ROOSTER full images and the FDK full images.

Motion analysis

The GTV centroid positions were calculated for all phases in order to assess the motion amplitudes (Fig. 1). For each combination of two phases the distance was calculated in three directions (superior-inferior [SI], anterior-posterior [AP], right-left [RL]). For each combination, the total 3D displacement vector length was calculated using the three calculated distances: $\sqrt{SI^2 + AP^2 + RL^2}$. Finally, the largest calculated displacement was selected to be the full 3D tumor motion amplitude.

Figure 1. Coronal view of a contoured GTV and both centroid positions for the 0% (solid line) and 50% (dotted line) phase. The corresponding 3D vector motion is noted additionally.

Results

4D image quality assessment

Visual inspection of the images as well as the image quality measures revealed that the MA-ROOSTER reconstructed images were close in image quality to the FDK images (Fig. 2; Fig. 3). This was more apparent for the patient group without metallic objects, as the metal hampered the image quality of both MA-ROOSTER and PC-FDK reconstructions (Pt. #1, Fig. 2; Fig. 3).

Figure 2. Visual comparison (coronal views) of one of the reconstructed phases of the MA-ROOSTER method compared to the same phase of the PC-FDK and FDK reconstructed images for two patients with differing image quality (pt. 1 suffering from additional image distortion). Quality measures for these reconstructions are shown below the figures. These include the contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR) and structural similarity index measures (SSIM). The centroid motion calculated between all phases for the shown treatment fractions of the two patients are noted additionally.

Figure 3. Image quality measures compared for the PC-FDK, MA-ROOSTER and FDK image reconstructions, assessed for two groups of five patients with and without metallic objects that caused image distortions. The box-plots are shown together with the median values. The lower box ranges from the first quartile to median, the upper box ranges from median to the third quartile. The lower and upper whiskers range from the first quartile and third quartile to the minimum and maximum values, respectively.

Figure 4. Range of GTV centroid motion amplitudes for each patient, measured on the daily 4DCBCT scans (box-plots), simulation 4DCTs and repeat 4DCTs (5/10 patients). The box-plots depict the first quartile to median (lower box) and median to third quartile (upper box). The lower and upper whiskers range from the first quartile and third quartile to the minimum and maximum values, respectively.

Motion evaluation

GTV centroid motion amplitudes of the 4DCBCTs after deformable contour warping are shown in Fig. 4. For the ten patients, median centroid motion amplitudes varied between 1.2 mm and 7.8 mm following the MA-ROOSTER method and varied between 1.7 mm and 17.3 mm for the PC-FDK reconstructions. The found motion amplitudes extended up till 37.5 mm for the PC-FDK method, as a result from the often poor image quality. Large motion amplitudes were also found for the MA-ROOSTER reconstructed images of patients #2 and #4, due to metallic implants hampering image quality. Pt. #10 showed a large decrease of tumor volume, which was also challenging for MA-ROOSTER. GTV centroid motion amplitudes of the simulation and repeat 4DCTs (pts. #1, #4, #7, #9, and #10) are additionally shown in Fig. 4. The MA-ROOSTER reconstructions were closer to the found motion of the 4DCTs compared to the PC-FDK reconstructions.

Discussion

This technical note showed that MA-ROOSTER is a feasible method to reconstruct 4DCBCT images in a clinical setting with sparse-view CBCT projection data acquired at a scanned proton gantry. MA-ROOSTER resulted in improved image quality compared to the conventionally used PC-FDK reconstruction approach, as phase-correlated methods suffer from under-sampling artifacts. This was found for a representative clinical dataset in terms of clinical characteristics and with a large variation between patients (e.g. presence of metallic objects). However, all patients were treated in the United States (US) at one PT institute, and therefore certain characteristics (e.g. weight, size, age) might differ for patients treated in other countries and/or PT institutes.

This improvement of MA-ROOSTER compared to PC-FDK was also in concordance with the findings reported in the SPARE challenge and other recent studies that compared an advanced reconstruction method to the conventional PC-FDK method [4, 13, 15].

The necessity of applying an advanced reconstruction method as the MA-

ROOSTER method was further demonstrated through deformable contour warping of the GTVs. GTV centroid motion amplitudes based on MA-ROOSTER reconstructions showed to be the most realistic.

One limitation is the absence of a ground truth to verify the exact daily motion. This could have been done using advanced techniques such as soft tissue tracking, or to simulate CBCT data including a ground truth motion. In a clinical setting however, the GTV motion will be relatively compared with the motion found during treatment simulation. The MA-ROOSTER reconstructed images showed sufficient image quality to be employed for this task, in contrary to the PC-FDK reconstructions.

It was shown that the ANACONDA algorithm handles CT-CBCT data well for contour warping, but we can assume that it is not as accurate as CT-CT DIR [21]. However, we consistently used this DIR algorithm for both MA-ROOSTER and PC-FDK reconstructions on the same patient data set, thus can compare the two methods with the same DIR accuracy.

Despite that the MA-ROOSTER found motion was the closest to the range of motion found for the 4DCTs, differences remained as the two modalities differ in image quality [17]. Manual checking of contours in 4DCBCTs after deformable warping could improve the motion estimation. This was not performed for the purpose of this study to objectively compare the image quality and measured motion. Other factors like tumor growth, tumor shrinkage or pleural effusion could also result in differences in measured motion, especially between the simulation 4DCT and daily 4DCBCTs.

Generally, the image quality should always be evaluated in the context of the image purpose. MA-ROOSTER reconstructed 4DCBCTs were found suitable in our opinion in the context of tumor motion assessment. For more advanced applications, as for example 4DCBCT-based proton dose calculations, further improvements will be required to warrant sufficient image quality. The finite range of protons and their sensitivity to changes in water equivalent thickness make it important to monitor variations in motion of the tumor and surrounding

tissue. Especially when variations occur in the beam paths, at the distal edge or the lateral penumbra regions. High quality 4DCBCT reconstructions will therefore be of interest to monitor the anatomical and motion differences accurately.

The reconstruction workflow used for this research is a semi-automatic workflow. We found an improved performance when visually checking and manually adjusting the otherwise automatically selected maxima and minima of the extracted respiratory signal during the phase binning process. The improvement was small which might justify skipping this manual intervention in favor of a fully automated workflow. Future work will investigate alternative methods for improved automatic phase binning, for example employ an external breathing signal.

Currently, the MA-ROOSTER workflow takes up to 40 minutes, which includes a 15-20 minutes preparation phase, during which the deformation vector fields between the 4DCT phases are computed as prior motion information. This preparation could also be done offline in advance. However, even the remaining 15-20 minutes for the 4DCBCT reconstruction itself are currently not suitable for an online employment. That means that 4DCBCT images will at first only be available for offline motion monitoring.

Further steps will be taken to improve the MA-ROOSTER reconstructions for motion monitoring and our future aim would be to implement MA-ROOSTER in the clinic.

Conclusion

The MA-ROOSTER reconstruction method performed well in terms of 4DCBCT image quality and GTV motion assessment. This was shown for a multifaceted, representative (N)SCLC patient data set acquired at a scanned proton gantry. MA-ROOSTER 4DCBCTs appear to be promising for daily 4DCBCT motion monitoring as part of a future adaptive PT workflow.

References

1. Landry G and Hua C ho. Current state and future applications of radiological image guidance for particle therapy. *Med Phys* 2018;45:e1086–e1095.
2. Feldkamp L, Davis L, and Kress J. Practical cone-beam algorithm. *J Opt Soc Am* 1984;1:612–9.
3. Mc Kinnon GC and Bates R. Towards Imaging the Beating Heart Usefully with a Conventional CT Scanner. *IEEE Trans Biomed Imaging* 1981:123–7.
4. Star-Lack J, Sun M, Oelhafen M, et al. A modified McKinnon-Bates (MKB) algorithm for improved 4D cone-beam computed tomography (CBCT) of the lung. *Med Phys* 2018;45:3783–99.
5. Jia X, Tian Z, Lou Y, Sonke JJ, and Jiang SB. Four-dimensional cone beam CT reconstruction and enhancement using a temporal nonlocal means method. *Med Phys* 2012;39:5592–602.
6. Chen GH, Tang J, and Leng S. Prior image constrained compressed sensing (PICCS): A method to accurately reconstruct dynamic CT images from highly undersampled projection data sets. *Med Phys* 2008;35:660–3.
7. Leng S, Tang J, Zambelli J, Nett B, Tolakanahalli R, and Chen GH. High temporal resolution and streak-free four-dimensional cone-beam computed tomography. *Phys Med Biol* 2008;53:5653–73.
8. Rit S, Wolthaus JW, Van Herk M, and Sonke JJ. On-the-fly motion-compensated cone-beam CT using an a priori model of the respiratory motion. *Med Phys* 2009;36:2283–96.
9. Li T, Koong A, and Xing L. Enhanced 4D cone-beam CT with inter-phase motion model. *Med Phys* 2007;34:3688–95.
10. Brehm M, Paysan P, Oelhafen M, and KachelrieSS M. Artifact-resistant motion estimation with a patient-specific artifact model for motion-compensated cone-beam CT. *Med Phys* 2013;40:1–13.
11. Chen M, Cao K, Zheng Y, and Siochi RAC. Motion-compensated mega-voltage cone beam CT using the deformation derived directly from 2D projection images. *IEEE Trans Med Imaging* 2013;32:1365–75.
12. Shrestha D, Tsai MY, Qin N, Zhang Y, Jia X, and Wang J. Dosimetric evaluation of 4D-CBCT reconstructed by Simultaneous Motion Estimation and Image Reconstruction (SMEIR) for carbon ion therapy of lung cancer. *Med Phys* 2019;46:4087–94.

13. Zhang H, Ma J, Bian Z, Zeng D, Feng Q, and Chen W. High quality 4D cone-beam CT reconstruction using motion-compensated total variation regularization. *Phys Med Biol* 2017;62:3313–29.
14. Park JC, Kim JS, Park SH, Liu Z, Song B, and Song WY. Motion-map constrained image reconstruction (MCIR): application to four-dimensional cone-beam computed tomography. *Med Phys* 2013;40:1–12.
15. Shieh CC, Gonzalez Y, Li B, et al. SPARE: Sparse-view reconstruction challenge for 4D cone-beam CT from a 1-min scan. *Med Phys* 2019;46:3799–811.
16. Mory C, Janssens G, and Rit S. Motion-aware temporal regularization for improved 4D cone-beam computed tomography. *Phys Med Biol* 2016;61:6856–77.
17. Niepel K, Kamp F, Kurz C, et al. Feasibility of 4DCBCT-based proton dose calculation: An ex vivo porcine lung phantom study. *Z Med Phys* 2019;29:249–61.
18. Rit S, Vila Oliva M, Brousmiche S, Labarbe R, Sarrut D, and Sharp GC. The Reconstruction Toolkit (RTK), an open-source cone-beam CT reconstruction toolkit based on the Insight Toolkit (ITK). *J Phys: Conf Ser* 2014;489:1–4.
19. Janssens G, Jacques L, Orban De Xivry J, Geets X, and MacQ B. Diffeomorphic registration of images with variable contrast enhancement. *Int J Biomed Imaging* 2011:1–16.
20. Zijp L, Sonke J, and Herk M van. Extraction of the respiratory signal from sequential thorax cone-beam X-ray images. In: *Proceedings of the 14th ICCR*. Seoul, Korea, 2004:507–9.
21. Weistrand O and Svensson S. The ANACONDA algorithm for deformable image registration in radiotherapy. *Med Phys* 2015;42:40–53.
22. Wang Z, Bovik AC, Sheikh HR, and Simoncelli EP. Image quality assessment: from error visibility to structural similarity. *IEEE Trans Image Process* 2004;13:600–12.

Chapter 5

Diaphragm based position verification to improve daily target dose coverage in proton and photon radiotherapy treatment of distal esophageal cancer

Abstract

Purpose

Modern conformal radiotherapy techniques have become highly relevant for the treatment of esophageal cancer, as the esophagus is surrounded by several critical organs at risk (OARs). The aim is to achieve adequate target dose coverage while reducing the dose to these OARs. However, the target coverage during treatment delivery is affected by target displacements and deformations and furthermore by density changes in the beam path due to variations in diaphragm position. We evaluated if the position of the diaphragm can be taken into account in position verification (PV) to optimize inter-fractional target dose coverage for esophageal cancer treatment.

Materials and Methods

Twenty treatment plans were computed for ten esophageal cancer patients: ten intensity modulated proton therapy (IMPT) and ten volumetric modulated arc therapy (VMAT) plans. Target coverage was inter-fractionally evaluated for these plans using different PV approaches based on: (1) bony anatomy (PV_B), (2) bony anatomy corrected for the diaphragm position (PV_BD) and (3) target volume (PV_T). To determine the correction needed to account for the diaphragm variation, inter-fractional displacements of the target volume were correlated with diaphragm displacements using repeated 4DCTs. The displacement analysis of the diaphragm was further extended based on daily acquired (4D)CBCTs in an inter- and intra-fractional context. This to assess the incidence and magnitudes of diaphragm variations, as well as the persistence of deviations throughout a treatment fraction.

Results

Inter-fractional target volume displacements were found to be the largest in the cranial-caudal direction (ranging from -6.5 to 13.5 mm). The cranial-caudal mean displacements ($r=0.838$), near-maximum displacements (95-percentile; $r=0.772$) and caudal border displacements ($r=0.729$) of the target correlated with displacements of the diaphragm. The cranial-caudal mean target displacement

was congruent with almost half of the diaphragm displacement ($y=0.439x$), which was used for the diaphragm correction in PV_BD. Target dose coverage using PV_B was adequate for patients with diaphragm displacements up till 12 mm (>94% of the dose in 98% of the volume). For larger displacements, the target coverage was better maintained by PV_T and PV_BD of which PV_BD accounted best for target displacements in combination with density variations ($D_{98\%}$: IMPT $95\% \pm 5\%$, VMAT $97\% \pm 6\%$). Similar incidence and extent of inter-fractional diaphragm shifts were found for 4DCTs and (4D)CBCTs. A diaphragm displacement of more than 12 mm was observed in 16% (4DCTs) and 20% ((4D)CBCTs) of the cases. Intra-fractional diaphragm monitoring showed systematic deviations through a treatment fraction, validating the need to correct for the diaphragm position.

Conclusion

For most cases, PV_B was sufficient to achieve adequate target dose coverage, but larger deviations of the diaphragm were best mitigated by PV_BD. To detect the cases where target dose coverage could be compromised due to diaphragm variations, we recommend monitoring of the diaphragm position prior to treatment through online imaging.

Introduction

For the treatment of esophageal cancer, chemoradiotherapy plays an important role in the definitive as well as in the pre-operative setting [1]. In radiotherapy, the aim is to achieve adequate target dose coverage while reducing dose to nearby organs at risk (OARs). Radiotherapy can be delivered using state-of-the-art photon therapy (e.g. volumetric modulated arc therapy [VMAT] or intensity modulated radiation therapy [IMRT]) or proton therapy (e.g. intensity modulated proton therapy [IMPT]) [2, 3]. These more conformal radiotherapy modalities are particularly relevant in the treatment of esophageal cancer, since the esophagus is surrounded by several critical OARs such as the lungs and the heart [4]. Reducing the dose to the OARs is associated with improved overall survival as the risk of treatment related pulmonary and cardiac complications reduces [5].

Radiotherapy in the thorax is challenged by motion and deformation of the anatomy, for example caused by respiration [6, 7]. For the treatment of distally located esophageal cancer, the diaphragm is a moving anatomical structure located in the beam path. A recent study by our group concluded that the variations of the diaphragm position can lead to deformations of the target volume and disturbances in the dose distribution, which consequently have a great impact on the target dose coverage in IMPT for distal esophageal cancer [8]. Similar outcomes were reported for IMRT and single field uniform dose (proton) plans [8]. To some degree, diaphragm variations can be accounted for during treatment planning by applying robust optimization and choosing beam angles that are more robust to diaphragm variations [9]. Additionally, comprehensive optimization strategies have been investigated to address the problem, including robust 4D optimization and the application of diaphragm density overrides, but these have also been found insufficient to cope with large diaphragm position variations [8, 10]. These approaches account for the diaphragm motion amplitude, but are not able to fully account for diaphragm position offsets.

It is essential to monitor the position of the diaphragm prior to treatment. Daily online imaging can be deployed to detect diaphragm variations using cone beam computed tomography (CBCT). This is particularly relevant for proton therapy, as protons are more sensitive to range and setup errors resulting in larger dose deviations [11]. In case of large diaphragm variations, plan evaluation that takes the actual anatomy into account is necessary to decide whether plan adaptation is required [12]. Re-planning is time and resource intensive, especially in proton therapy. Therefore, a method to improve target coverage on a daily basis is desired.

Image registration based on bony anatomy is common clinical practice for position verification (PV) for esophageal cancer [9, 13–16]. With upcoming 3D and 4D imaging techniques, several studies investigated motion and displacements of the target volume relative to bony anatomy and argued the added value of soft tissue matching [13, 17, 18]. However, the low contrast of

the CBCT in the mediastinum and abdominal region compromises accurate patient setup [13]. Improving the image quality of the CBCT will be often at the expense of additional daily imaging dose [19]. Fiducial markers could facilitate PV, but have been found insufficient to rely on completely due to tissue deformation, visibility and marker migration, and have the disadvantage of adding an invasive procedure [15, 18]. Additionally, the markers could create artifacts, compromising diagnostic and dosimetric accuracy [20]. However, for the purpose of motion evaluation, fiducial markers facilitated detailed inter- and intra-fractional analysis of the gross tumor volume (GTV). Multiple studies showed that the largest motion occurs in the lower part of the esophagus and proximal stomach and predominantly in the cranial-caudal direction [15, 18–21]. Furthermore, studies have shown that the target volume moves congruently with the diaphragm [22, 23]. Therefore, we hypothesized that the position of the diaphragm can be used to improve alignment of the target volume. An additional result would be that the densities in the beam path would be more similar to the planning situation. The first objective of this study was to investigate to what extent target volume displacements correlate with diaphragm variations. The daily diaphragm position served as input to improve alignment of the target volume during PV (based on bony anatomy). In addition, the incidence and magnitude of the diaphragm variations during the whole treatment course was assessed by daily CBCT imaging. The intra-fractional reproducibility of the diaphragm position was specifically assessed to evaluate the persistence of diaphragm variations throughout a treatment fraction and to validate the applicability of a diaphragm-based correction. Finally, a dosimetric analysis was employed to evaluate if the proposed PV method would result in target dose coverage improvement compared to a bony anatomy or target volume match.

Methods and Materials

Patient data

A prospective cohort pilot study (REACT, ClinicalTrials.gov Identifier NCT03024138) of 20 consecutive patients provided a unique dataset consisting of weekly repeated 4D computed tomography (CT) and daily (4D)CBCT data for esophageal

cancer patients. A second (4D)CBCT was acquired at the end of each treatment fraction twice a week. The 4DCTs and 4DCBCTs were reconstructed into ten breathing phases following phase-based binning and for each set an average (CB)CT was created. The treatment duration was either five or six weeks, depending on the dose prescription (4140 cGy(RBE) or 5040 cGy(RBE), respectively; RBE=1.1 for proton treatment plans). Ten distal esophageal cancer patients were selected from the cohort. For two patients, seven weekly 4DCTs were available, for seven patients six 4DCTs and for one patient five 4DCTs. For one patient, the repeated 4DCT of the first week of treatment was selected as the planning CT, as the original planning 4DCT contained major artifacts.

Data preparation

For all available average CT scans, a clinical target volume (CTV) was created by a 30-mm extension in cranial-caudal direction of the GTV of the primary tumor plus a 7-mm isotropic expansion of the GTV of the lymph nodes. Additionally, the fatty mediastinal tissue was included in the CTV along the target length. The CTV contour was subsequently checked and manually expanded for all breathing phases of the corresponding 4DCT to create the internal target volume (ITV). Finally, a planning target volume (PTV) for photon treatment planning was created by an isotropic 8 mm expansion of the ITV.

Correlations CTV and diaphragm displacements

The correlation between inter-fractional displacements of the target volume and the diaphragm was assessed. PV was rigidly performed based on the bony anatomy (PV_B), where a box region was created around the vertebrae at the cranial-caudal level of the target to serve as the region of interest (ROI) during image registration (Fig. 1). The registration was performed between each average weekly repeated 4DCT and the average planning 4DCT. Afterwards, a deformable image registration (DIR) was applied between the end-of-expiration phase of each weekly repeated 4DCT and the end-of-expiration phase of the planning 4DCT using the Anaconda DIR available in RayStation (RaySearch Laboratories, Stockholm, Sweden), with the CTV as controlling ROI [24]. The

resulting deformation vectors were evaluated in all cardinal directions using an in-house developed script. Four parameters were defined and calculated: the mean CTV displacement, the 95-percentile (near-maximum) CTV displacement, the cranial CTV border displacement and lastly the caudal CTV border displacement.

Figure 1. Sagittal view of a representative patient presenting the different ROIs for image registration. The planning target volume (PTV, orange) and internal target volume (ITV, blue) are shown, as well as the box used as ROI during PV_B (green).

Position verification method comparison

Three different PV methods were evaluated that were all based on image registration. The image registrations were performed in RayStation with six degrees of freedom. All three methods simulated PV at the treatment machine by registering the averages of the repeated 4DCTs to the average planning CT. The first method was based on bony anatomy (PV_B), as previously described. The second method was based on the bony anatomy match, with an additional shift to account for the change in position of the left diaphragm relative to the bony anatomy (PV_BD). Only the cranial-caudal displacement was taken into account, as previous studies showed that displacement particularly occurs in this direction [17–20, 23]. The cranial-caudal difference between the bony anatomy match and the diaphragm match was determined by shifting the bony anatomy match in cranial-caudal direction to the level where the left diaphragm domes matched. PV was subsequently performed using the bony anatomy match plus a cranial-caudal shift of

a size that is determined by the correlation between the diaphragm and the target volume displacement, as described in the section above. The third method (PV_T) consisted of registering the target, by appointing the PTV as ROI during image registration (Fig. 1).

Inter- and intra-fractional diaphragm reproducibility

Additionally, inter- and intra-fractional baseline shifts of the left diaphragm relative to the bony anatomy were investigated to a greater extent by performing PV for the averages of the 4DCBTs or the available 3DCBTs. This was done for both pre- and post-treatment CBCTs to investigate the inter- and intra-fractional reproducibility of the diaphragm position.

Treatment planning

Clinically approved VMAT and IMPT plans were created on the average planning CT in RayStation and the dose distributions were calculated with Collapsed Cone and Monte Carlo, respectively. All plans were optimized according clinical criteria to achieve acceptable target dose coverage ($D_{98\%} > 95\%$) and as low as possible OAR doses. The VMAT plans consisted of two full arcs with a beam energy of 6 MV. The plans were non-robustly optimized using the PTV and evaluated for its robustness by simulating 8.0 mm shifts after the nominal plan met all clinical criteria. IMPT treatment plans were created with typically two fields; one posterior and one right posterior oblique beam. The posterior beams were used to limit the influence of the diaphragm motion [25]. The IMPT treatment plans were robustly optimized using the ITV. The nominal plan was optimized to meet the same criteria concerning OAR doses as the corresponding VMAT plan. Next, robustness evaluation for the IMPT plans was performed by simulating setup uncertainties of 8.0 mm and range errors of $\pm 3\%$. The same criteria were used for both VMAT and IMPT for the resulting voxel-wise minimum ($Vw_{\min}$) and maximum ($Vw_{\max}$) dose distributions from the robustness evaluation [24]. The first criterion was that the dose to 98% of the ITV volume ($D_{98\%}$) had to be at least 95% of the prescription dose in the $Vw_{\min}$ dose distribution. For the $Vw_{\max}$ dose distribution, hotspots below 110% and 115% of the prescribed dose were allowed to 2cc and

Occ within the body volume, respectively.

Inter-fractional dosimetric assessment

Inter-fractional robustness of all treatment plans for every PV method was evaluated by simulating errors in setup (2.0 mm) (for both VMAT and IMPT) and range ($\pm 3\%$) (for only IMPT) on the average image of each weekly repeated 4DCT. The 2.0 mm error shift accounts for the residual errors that still exist during treatment after online position correction based on CBCT, such as intra-fractional motion and uncertainties in isocenter position and other mechanical uncertainties of the imaging and treatment systems [10, 12]. Target coverage was evaluated by the $D_{98\%}$ of the ITV on the resulting $V_{w_{min}}$ dose distribution [24]. A minimum ITV dose coverage ($D_{98\%}$) of 94% of the prescribed dose was considered clinically acceptable for the repeated CTs [12].

Results

Correlations CTV and diaphragm displacements

The inter-fractional CTV displacements for the weekly 4DCTs ranged between -1.2 and 3.3 mm (median: 0.0 mm) for the left-right direction, -6.6 mm and 2.6 mm (median: -0.7 mm) for the anterior-posterior direction and between -6.5 and 13.5 mm (median: -0.2 mm) for the cranial-caudal direction. Four parameters were specifically investigated for these translational directions; the mean, the near-maximum (95-percentile), the cranial border and the caudal border displacement of the CTV. Fig. 2 shows significant and strong correlations for the cranial-caudal CTV displacement and the diaphragm displacement for all parameters, meaning that the CTV volume is moving congruently with the diaphragm in cranial-caudal direction. A negative and moderate correlation was found for the anterior-posterior CTV displacement, meaning that the CTV volume is often moving posteriorly where the diaphragm is moving cranially. Weak and non-significant correlations were found for the left-right CTV displacement, except for the near-maximum left-right displacement ($r = .408$, $p = .003$; Fig. 2). Overall, the strongest correlations were found for the mean CTV displacement, followed

by the near-maximum and the caudal border displacement. Displacements of the cranial border remained small in all cardinal directions. Fig. 3 visualizes two examples of CTV displacements together with two large oppositely displaced diaphragms. This figure shows that the largest CTV displacements are found just below the diaphragm in the region of the gastro esophageal junction (GEJ). The inter-fractional CTV displacement analysis was performed to establish an additional shift to PV_B to perform PV_BD. We found that almost half of the cranial-caudal diaphragm displacement was congruent to the cranial-caudal mean CTV displacement ($y = 0.439x$; Fig. 2) and decided to use half of the cranial-caudal diaphragm displacement to perform PV_BD.

Figure 2. Inter-fractional analysis of the CTV displacement and correlations with the diaphragm displacement for cranial-caudal (CC, purple), anterior-posterior (AP, blue) and left-right (LR, green) directions. Investigated displacement parameters are the mean, the near-maximum (95-percentile), the cranial border and the caudal border of the CTV.

Figure 3. Coronal views of the CTV and diaphragm contours for two sample cases (patient 9 - week 0 vs. week 1, patient 4 - week 0 vs. week 3). Large inter-fractional diaphragm displacements are observed in opposite directions, which caused congruent CTV displacements, most apparent in the GEJ region and the caudal border.

Position verification method comparison

Fig. 4A shows the resulting couch translations for each of the PV methods. The translations were the largest for the cranial-caudal (up to 20 mm) and left-right (up to 16 mm) directions, compared to the anterior-posterior (up to 8 mm) direction. Differences between the registration methods were usually small for the anterior-posterior and the left-right direction, but substantial for the cranial-caudal direction (up to 6 mm differences). In several cases, the cranial-caudal translation for PV_B and PV_BD, and PV_T were even in opposite direction. In general, the applied rotations were larger for the PV_T method compared to the PV_B and PV_BD methods (Fig. 4B), with differences in couch corrections up to 1.9°, 0.9° and 1.0° for pitch, roll and yaw, respectively.

Inter- and intra-fractional diaphragm reproducibility

The inter- and intra-fractional reproducibility of the diaphragm was analysed using repeated (4D)CBCT and 4DCT data. For each patient, displacements of the diaphragm relative to bony anatomy during the whole treatment course are presented in Fig. 5. For some patients, a trend of increasing or decreasing diaphragm displacements is clearly visible (patient 1-4), where others remain fairly constant (patient 6-8, 10) during treatment. Patient 1, 5 and 9 showed a larger and varying

Figure 4. The required translations (A) and rotations (B) for each PV method. Note that only the cranial-caudal component was changed from the PV_B method to the PV_BD method.

range of displacements throughout the treatment course. The displacements of all patients are additionally summarized in the two histograms, showing a greater extent of diaphragm displacements inter-fractionally. Results of the inter-fractional displacement range using the 4DCT or 4DCBCT for all measurements were similar (respectively 57% and 55% ≤ 4.0 mm). Intra-fractional displacements, as observed in the CBCT images, remained usually small (76% of all treatment fractions ≤ 4.0 mm), where both small and large deviations persisted through a treatment fraction for most cases. There was no trend seen in

deviations getting smaller or larger intra-fractionally for initially small and large deviations independently. Patient 3 showed for two fractions a pre-treatment fraction shift of less than 12 mm, that increased beyond 12 mm post-treatment fraction. Patient 9 showed for three treatment fractions an initial displacement up till 30 mm, which was decreased to less than 12 mm after the treatment fraction. Five patients showed consistent intra-fractional drifts of the diaphragm, where for two patients almost all deviations increased during the fraction. Furthermore, it can be observed that cranial displacements of the diaphragm occurred more often than caudal displacements (47% and 68% cranial inter- and intra-fractional displacements, respectively), which means that the initial cranial offset of the diaphragm tends to get worse intra-fractionally, whereas negative offsets tend to reduce during a fraction. Diaphragm displacements beyond 12.0 mm occurred in 16% of the (4D)CBCTs prior to a treatment fraction compared to 20% in the 4DCTs.

Dosimetric evaluation of PV methods

The ITV dose coverage for the three different PV approaches was analysed by means of the $D_{98\%}$ in the $V_{w_{min}}$. The weekly robustness evaluations together with the left diaphragm baseline displacements are shown in Fig. 6. For most cases (42/51 IMPT; 44/51 VMAT), PV_B was sufficient to achieve adequate ITV coverage ($D_{98\%} \geq 94\%$ of the prescribed dose). In the failing cases, diaphragm variations of more than 12 mm occurred. For deviations up to 16 mm, PV_BD and PV_T were able to restore the target coverage loss to the acceptance level of 94%. Table 1 shows that on average the dose coverage for both the IMPT and VMAT plans was best for the PV_BD method. For patient 9, where diaphragm deviations of more than 16 mm occurred, acceptable target dose coverage could not be reached in any of the evaluations. However, improvement of the target coverage were found for this patient using PV_BD and PV_T, compared to PV_. The last weekly evaluation of patient 3 was the only case where the target dose coverage was found worst for the PV_BD method and best for the PV_T method. A visualisation of the target coverage for the three PV methods is included in Fig. 7. There, it can be observed that a caudal diaphragm offset resulted in target coverage loss at the cau-

dal border of the CTV, as well as a dose increase in the diaphragm region next to the heart. Cranial diaphragm offsets resulted in even more target dose coverage loss, appearing in the diaphragm region. Both the underdosage and overdosage regions were reduced when using PV_BD or PV_T, compared to PV_B.

Figure 5. Inter- and intra-fractional displacements of the left diaphragm relative to bony anatomy using 4DCT and (4D)CBCT data for each patient throughout the treatment course. The dotted line represents the threshold (12 mm) when diaphragm variations could lead to underdosage of the target volume. Combined intra- and inter-fractional displacements for the CBCT data are additionally shown in two histograms.

Table 1. Averaged results of the weekly target dose coverage ($D_{98\%}$)

	$D_{98\%}$ (mean $\pm$ SD)		
	PV_B	PV_BD	PV_T
IMPT	91% $\pm$ 15%	95% $\pm$ 5%	92% $\pm$ 12%
VMAT	95% $\pm$ 9%	97% $\pm$ 6%	96% $\pm$ 9%

Figure 6. Inter-fractional robustness evaluation of the target coverage ($D_{98\%}$ [%]) of the ITV against diaphragm baseline shifts for both IMPT and VMAT treatments and for the three PV methods. The dotted line represents the acceptance level of 94% dose coverage. Negative shifts of the diaphragm represent a caudal displacement.

Figure 7. Dosimetric results for patient 9 and patient 4, showing a cranial and caudal diaphragm offset, respectively. The voxel-wise minimum dose (Vw_{min}), which is evaluated for the target (ITV, blue) dose coverage, is shown in the coronal plane and the nominal dose which is evaluated for the OARs (heart, red) is shown in the axial plane. The 94% and 107% dose is shown in green and orange, respectively. The cranial offset resulted in target dose coverage loss in the GEJ region for both IMPT and VMAT for PV_B. The caudal offset of the diaphragm resulted in target coverage loss at the caudal border of the ITV and overdosage at the heart region for both modalities for PV_B. For both patients and both modalities, PV_BD and PV_T were able to restore most of the target coverage loss and reduce undesired high dose regions outside the target.

Discussion

This study shows the impact of diaphragm variations on proton and photon target dose coverage, and the influence of different PV methods. Generally, both

IMPT and VMAT proved to be sufficiently robust modalities for radiotherapy treatment of esophageal cancer. For most cases, the conventional PV_B is sufficient to achieve good target dose coverage. Diaphragm deviations up to 12 mm ensured a target dose coverage of at least 94% by the PV_B method. For these cases, PV_BD and PV_T performed equally well. Differences between the three investigated PV methods were only observed for diaphragm displacements of more than 12 mm, when the PV_B method was not found sufficient anymore. The PV_BD and PV_T method showed an improvement of the target dose coverage for these cases compared to PV_B. Patient 9 is an example where re-planning was necessary regardless of the chosen PV method. For this patient, the PV_BD restored the target dose coverage best and would be appropriate as a temporarily solution until the adapted plan is available. Generally, the PV_BD method was found suitable in almost all cases. PV_T is the preferred method when the diaphragm is not clearly visible, which occurred in the last treatment weeks of patient 3 due to pleural effusion.

The effect of diaphragm offsets on the target dose coverage was larger for the cranial offset of the diaphragm compared to caudal offsets. For both directions, target deformation occurred, where the cranial shift of the diaphragm additionally resulted in increase of tissue densities in the beam path. As expected, VMAT was less sensitive to these density changes than IMPT. The increased density changes caused underdosage in the GEJ region, where potentially also the target dose coverage of the GTV could be affected. The caudal diaphragm offset caused underdosage at the caudal CTV border and beam overshoots. This mainly resulted in increased heart dose, due to the use of posterior beams in IMPT and hotspots that arose near the heart in VMAT. Similar target coverage loss and increased heart dose due to diaphragm variations has been reported by Nyeng et al. [9], which could clinically result in lower tumor control and increased risk of cardiac complications.

The CBCT-based intra-fractional displacement analysis showed that diaphragm displacements pre-treatment were usually still present post-treatment. This confirms that the measured pre-treatment diaphragm position remains rela-

tively constant during a fraction, potential target dose coverage loss (caused by the diaphragm deviation) persists and an additional correction indeed is beneficial. Nevertheless, (smaller) displacements tend to occur both intra- and inter-fractionally, so we advise to apply a threshold with regard to the diaphragm position correction rather than applying a correction as a default.

The CBCT-based motion analysis showed that inter-fractional cranial displacements of the diaphragm occurred more often than caudal displacements, and also were more likely to deviate further during a fraction. Cranial offsets especially have the risk to result in dose deviations. Generally, displacements seen in the 4DCTs followed the same trend as displacements seen in the 4DCBCTs. Monitoring diaphragm positions is essential to evaluate trends and the need for re-planning. Incidental deviations occurred, emphasizing the added value of the PV_BD method, to be able to handle deviations online in an efficient way. Additionally, in case of persistent small deviations, applying PV_BD could avoid the need for re-planning. Applying efficient daily diaphragm correction during PV becomes increasingly relevant to improve daily dose delivery in the context of more conformal treatments, margin reductions and hypofractionation.

Many inter- and intra-fractional motion analyses in esophageal cancer have been described in literature [15–18, 21]. However, only a few studies describe the actual dosimetric effect of motion and displacements for this indication. This study shows the dosimetric impact of displacements of the target, and also the clearly relevant influence of changing anatomy outside the target. Markers and 4D imaging have facilitated accurate motion monitoring, mainly focusing on the GTV. However, the targeted volume is the CTV, which is usually extended outside the GTV by 30 mm in cranial-caudal direction and might therefore show different motion characteristics. For the CTV, we found, congruent with previous studies that the largest inter-fractional displacement occur in cranial-caudal direction, followed by the anterior-posterior direction [15–17, 21]. These displacements were usually found in the GEJ region. Like Wang et al. [22], we concluded that the diaphragm could be a good surrogate for displacements in the GEJ region. However, other parts of the CTV shift in less extent and as Vocken et al. [18]

showed, the diaphragm can not be used as a full displacement surrogate for the entire target in esophageal cancer patients.

The line fitted through the mean CTV displacement as a function of the diaphragm displacement in the cranial-caudal direction had a slope of 0.439. Therefore, the CTV displacement was on average equal to 0.44 times the diaphragm displacement. We decided to round this up to half of the diaphragm displacement as the correction measure in PV_BD, as this is more practical to implement in clinical practice. Our detailed motion analysis revealed that the cranial border is less subject to diaphragm displacements. Therefore, caution has to be taken not to shift the isocenter too far to prevent cranial miss. However, other parts of the CTV might profit from an extended correction. In our patient group, the isocenter was never shifted more than 8 mm in caudal direction (which complies with the ITV-PTV margin, e.g. robustness settings). Further analysis is necessary to determine whether thresholds need to be defined. Also, the target coverage is not only influenced by the diaphragm position. Other factors, for example gastric filling, mediastinal changes and pleural effusion can also influence the target coverage [9, 26]. All these disturbing factors highlight the importance of repeated imaging.

Not only the target should be aligned during PV, but also density changes in the beam path have to be accounted for, especially in proton therapy. In the current beam setup for IMPT, potential misalignment of the bony anatomy in the beam can lead to disturbances in the dose distribution. Additionally, diaphragm variations causes density changes in the beam paths for both IMPT and VMAT. As this was better accounted for using the PV_BD method, this could explain the superiority of the PV_BD method compared to the PV_T method.

For our study, repeated 4DCTs were used for image registration and to assess the dosimetric impact of diaphragm displacements and different PV methods. However, the actual PV takes place between the average planning CT and the CBCT acquired prior to treatment, with different image registration algorithms and less soft tissue contrast compared to repeat CTs [13]. Especially the described

PV_T method could become unsuitable, as the registration is susceptible to inaccurate soft tissue matching. However, in the study of Hoffmann et al. [17] all automatic soft tissue matches based on the CTV were manually checked and no corrections were indicated. Moreover, the PV_T resulted in increased rotational shifts of the treatment couch to account for larger target deformations, similar to the results of Hawkins et al. [13]. Besides impractical reasons of larger rotations in terms of collisions and limitations of application on the treatment machine, larger residual errors were found for patients without fixation to the treatment couch, if larger pitch and roll rotations are applied [27]. Still, it is important to note that we found a benefit of PV_T compared to PV_B, which is in accordance with previous studies [13, 17].

We chose to focus on the diaphragm position in the expiration phase, as the highest border of the diaphragm is the easiest region to interpret on the (CB)CTs, regardless if it is 3D or 4D. More importantly, the most cranial position of the diaphragm proved to be the most important to detect increased tissue densities in the beam path. Moreover, we chose to focus on the left diaphragm, as esophageal tumors are usually more oriented to the left side. However, in the context of increased densities in the beam path, the position of the right diaphragm might be equally important, especially for the used beam setup of IMPT. However, A previous study confirmed similar displacement patterns of the right and left diaphragm, thus we assume that this would have little effect on the outcomes presented here [8].

Based on our findings, we recommend using online imaging and PV based on bony anatomy initially for both IMPT and VMAT in the treatment of distal esophageal cancer. Using (CB)CT, the position of the diaphragm can be subsequently visualized and checked. As the target dose coverage was affected for diaphragm variations of more than 12 mm, an additional shift (PV_BD) could be applied to achieve the most optimal target dose coverage. Especially cases showing a cranial displacement of the diaphragm could profit from this method. For incidental and moderate diaphragm deviations up to 16 mm, PV_BD can restore most of the target coverage loss and eliminate the need for re-planning.

For persistent and large diaphragm deviations (>16 mm), PV_BD showed to improve the target coverage best and could serve as temporarily solution until re-planning has been performed.

Conclusion

Position verification in VMAT and IMPT for esophageal cancer based on bony anatomy can be improved with an additional diaphragm position correction in case of larger diaphragm displacements (>12 mm). Better target dose coverage can be achieved compared to image registration based on bony anatomy alone or based on the target.

References

1. Lloyd S and Chang BW. Current strategies in chemoradiation for esophageal cancer. *J Gastrointest Oncol* 2014;5:156–65.
2. Martin S, Chen JZ, Rashid Dar A, and Yartsev S. Dosimetric comparison of helical tomotherapy, RapidArc, and a novel IMRT & Arc technique for esophageal carcinoma. *Radiother Oncol* 2011;101:431–7.
3. Welsh J, Gomez D, Palmer M, et al. Intensity-modulated proton therapy further reduces normal-tissue exposure during definitive therapy for locally advanced distal esophageal tumors: a dosimetric study. *Int J Radiat Oncol Biol Phys* 2011;81:1336–42.
4. Verma V, Moreno AC, and Lin SH. Advances in radiotherapy management of esophageal cancer. *J Clin Med* 2016;5:1–11.
5. Xu C, Guo L, Liao Z, et al. Heart and lung doses are independent predictors of overall survival in esophageal cancer after chemoradiotherapy. *Clin Transl Rad Oncol* 2019;17:17–23.
6. Bert C and Durante M. Motion in radiotherapy: particle therapy. *Phys Med Biol* 2011;56:113–44.
7. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874–900.
8. Visser S, Neh H, and Ribeiro C. Can we use the same planning strategies for diaphragm motion in IMPT as we use in VMAT? Abstract 2020.

9. Nyeng TB, Nordsmark M, and Hoffmann L. Dosimetric evaluation of anatomical changes during treatment to identify criteria for adaptive radiotherapy in oesophageal cancer patients. *Acta Oncol* 2015;54:1467–73.
10. Ribeiro C, Meijers A, Korevaar E, et al. Comprehensive 4D robustness evaluation for pencil beam scanned proton plans. *Radiother Oncol* 2019;136:185–9.
11. Engelsman M and Kooy HM. Target volume dose considerations in proton beam treatment planning for lung tumors. *Med Phys* 2005;32:3549–57.
12. Anakotta RM, Laan HP van der, Visser S, et al. Weekly robustness evaluation of intensity-modulated proton therapy for oesophageal cancer. *Radiother Oncol* 2020;151:66–72.
13. Hawkins MA, Aitken A, Hansen VN, McNair HA, and Tait DM. Cone beam CT verification for oesophageal cancer - impact of volume selected for image registration. *Acta Oncol* 2011;50:1183–90.
14. Chen YJ, Han C, Liu A, et al. Setup variations in radiotherapy of esophageal cancer: evaluation by daily megavoltage computed tomographic localization. *Int J Radiat Oncol Biol Phys* 2007;68:1537–45.
15. Jin P, Horst A van der, Jong R de, et al. Marker-based quantification of interfractional tumor position variation and the use of markers for setup verification in radiation therapy for esophageal cancer. *Radiother Oncol* 2015;117:412–8.
16. Jin P, Hulshof MCCM, Wieringen N van, Bel A, and Alderliesten T. Interfractional variability of respiration-induced esophageal tumor motion quantified using fiducial markers and four-dimensional cone-beam computed tomography. *Radiother Oncol* 2017;124:147–54.
17. Hoffmann L, Poulsen PR, Ravkilde T, et al. Setup strategies and uncertainties in esophageal radiotherapy based on detailed intra- and interfractional tumor motion mapping. *Radiother Oncol* 2019;136:161–8.
18. Voncken F, Nakhaee S, Stam B, et al. Voncken.pdf. *Pract Radiat Oncol* 2020;10:84–92.
19. Siewerdsen JH and Jaffray DA. Optimization of x-ray imaging geometry (with specific application to flat-panel cone-beam computed tomography). *Med Phys* 2000;27:1903–14.
20. Habermehl D, Henkner K, Ecker S, Jäkel O, Debus J, and Combs SE. Evaluation of different fiducial markers for image-guided radiotherapy and particle therapy. *J Radiat Res* 2013;54:61–8.

21. Jin P, Hulshof MCCM, Jong R de, Hooft JE van, Bel A, and Alderliesten T. Quantification of respiration-induced esophageal tumor motion using fiducial markers and four-dimensional computed tomography. *Radiother Oncol* 2016;118:492–7.
22. Wang J, Lin SH, Dong L, et al. Quantifying the interfractional displacement of the gastroesophageal junction during radiation therapy for esophageal cancer. *Int J Radiat Oncol Biol Phys* 2012;83:273–80.
23. Roos CT, Faiz Z, Visser S, et al. A comprehensive motion analysis consequences for high precision image-guided radiotherapy of esophageal cancer patients. *Acta Oncol* 2020:4–12.
24. Korevaar EW, Habraken SJM, Scandurra D, et al. Practical robustness evaluation in radiotherapy - a photon and proton-proof alternative to PTV-based plan evaluation. *Radiother Oncol* 2019;141:267–74.
25. Yu J, Zhang X, Liao L, et al. Motion-robust intensity-modulated proton therapy for distal esophageal cancer. *Med Phys* 2016;43:1111–8.
26. Møller DS, Alber M, Nordsmark M, Nyeng TB, Lutz CM, and Hoffmann L. Validation of a robust strategy for proton spot scanning for oesophageal cancer in the presence of anatomical changes. *Radiother Oncol* 2019;131:174–8.
27. Guckenberger M, Meyer J, Wilbert J, Baier K, Sauer O, and Flentje M. Precision of image-guided radiotherapy (IGRT) in six degrees of freedom and limitations in clinical practice. *Strahlenther Onkol* 2007;183:307–13.

Chapter 6

Summarizing discussion and future perspectives

Summarizing discussion and future perspectives

This thesis addressed a number of important aspects related to motion monitoring for moving targets in the context of pencil beam scanned proton therapy (PBS-PT) for intrathoracic tumours. The first two chapters examined whether daily motion monitoring is necessary for non-small cell lung cancer (NSCLC) patients that are treated either during breath-hold or free breathing. First, the lung anatomy reproducibility of breath-holding using the Active Breathing Coordinator (ABC) control was investigated. ABC controlled breath-holding is an effective technique for motion mitigation and this technique would be a relevant option for lung tumours with extensive motion (big movers). In parallel with this project in chapter 2, an analysis of lung tumour motion and lung tumour motion variations on a weekly and daily basis was conducted in chapter 3. We found that even after selecting patients exhibiting tumour motion of less than 5 mm at the treatment planning stage, one third of the patients showed larger tumour motion during the course of treatment. These findings stress the importance of monitoring tumour motion on a daily level, which can be done through 4D conebeam CT (4DCBCT) imaging. 4DCBCT imaging does not only provide internal motion information, but also internal anatomical information. Internal anatomical information is particularly important for scanned proton treatments because this technique is sensitive to changes in water equivalent path length. As 4DCBCT reconstruction software is not yet available for commercial scanned proton gantry systems (only 3DCBCT reconstruction software), an automated workflow was produced in chapter 4 to reconstruct sparse-view CBCT projection data into 4DCBCT scans. This workflow included an advanced reconstruction technique to manage the sparse projection data. 3DCBCT imaging was already performed on a daily basis for position verification before each fraction of treatment. Therefore, we conducted a study for esophageal cancer patients to investigate the potential of a diaphragm position check with a possible position correction. This was done to improve the robustness of PBS-PT treatment to larger daily deviations in diaphragm position and consequently the misalignment of the tumour position. This work has been described and discussed in chapter 5.

Reproducibility of the lung anatomy under active breathing coordinator control

Chapter 2 describes a thorough evaluation of the lung anatomy reproducibility under ABC control, including a simulation of possible dosimetric consequences for robust optimized PBS-PT treatments. Our study is one of few published studies that have shown that the breath-hold method is a feasible motion mitigation technique during IMPT PBS-PT treatment for NSCLC patients. In this section, a number of aspects will be addressed that are still important to discuss or investigate further when considering the breath-hold method.

The aim of our study was to investigate the anatomical reproducibility of ABC controlled breath-holding. The ABC device assists breath-holding by controlling the volume of air that is inspired at a given threshold value. Kaza et al. [1] reported lung volume reproducibility during repeated breath-holding using the ABC device. However, this does not necessarily mean a reproducible anatomy. For PBS-PT implementation it is necessary to gain more insight into the possible target position variations between breath-holds. These uncertainties can be accounted for during robust treatment planning. Our study confirmed that breath-hold under ABC control is a reproducible technique, with median lung anatomy displacements of 1.6 mm inter-fractionally and 1.3 mm intra-fractionally between breath-holds. We evaluated the dosimetric consequences of the anatomical reproducibility for robust optimized IMPT PBS-PT treatment plans with a 5 mm setup margin and 3% range error. We found that 22 out of 23 simulated breath-hold scenarios were robust to the breath-hold reproducibility uncertainties (minimally 95% of the prescribed dose [60 Gy] to 98% of the target volume). Furthermore, dose increases were only found up to a maximum of 110% of the prescribed dose for the target volumes. Finally, minimal dosimetric differences were found for the organs at risk.

Recently, two other studies have been published that investigated the target or lung anatomy reproducibility under breath-hold for NSCLC patients. Gorgisyan et al. [2] acquired a planning breath-hold CT scan and nine repeated breath-hold CTs for 15 patients with moderate to large NSCLC target volumes. Water equiva-

lent path length differences were found of >3 mm for more than 15% of the target volume voxels in 6 out of 15 patients. This translated into a decrease of $>5\%$ of the target volume receiving 95% of the prescribed dose ($V_{95\%}$) for the intensity modulated proton therapy (IMPT) 3-field plans in only three patients. Therefore, they concluded that, for most patients, IMPT treatment is robust to breath-hold uncertainties. Scherman-Rydhög et al. [3] investigated position variations of NSCLC tumours and mediastinal lymph nodes during breath-hold using liquid fiducial markers. They showed that the inter-breath-hold uncertainties did not exceed 2 mm for most of the measurements. Furthermore, the authors quantified the large reduction in respiratory motion when using visually guided breath-hold compared to free breathing (3.3 mm [anterior-posterior], 2.1 mm [left-right], 6.4 mm [superior-inferior]). Findings of these recent studies and the published studies as discussed in chapter 2 are in line with our measured displacements and dosimetric results.

Residual intra-breath-hold motion has not been investigated in chapter 2. Gorgisyan et al. [4] experimentally evaluated the robustness of single field uniform dose and IMPT PBS-PT treatments to target position drifts during breath-hold. The intra-breath-hold motion was measured for three patients using fluoroscopic marker imaging. The fluoroscopy motion data was then transferred to an anthropomorphic breathing phantom for further dosimetric investigation. They found that only the single field uniform dose plans were robust to intra-breath-hold target position uncertainties. They suggested using multiple motion mitigation techniques for IMPT PBS-PT treatments, such as rescanning in combination with breath-holding. The intra-breath-hold uncertainties were relatively small compared to inter-breath-hold uncertainties. However, even small variations in target position during one specific breath-hold can cause interplay effects. This might explain why the IMPT treatments were not entirely robust to intra-breath-hold variations of the target position. It should be noted that this research was conducted for only one simulated treatment fraction and for a very limited number of cases (four primary tumours). Rescanning provides a feasible option for reducing interplay effects resulting from intra-breath-hold motion, with the disadvantage that rescanning prolongs the treatment delivery

time [5, 6].

Robust optimization improves the robustness of IMPT PBS-PT treatment to both intra-breath-hold and inter-breath-hold target position variations. In the consensus guidelines published in 2017, the Particle Therapy Co-Operative Group suggested using setup uncertainties of 5 mm or more, and creating an internal gross tumour volume based on multiple breath-hold CT scans [7]. In chapter 2 we only used the first acquired breath-hold scan for target volume definition and either 3 mm or 5 mm setup uncertainties, thus creating less robust treatment plans than advised. Nevertheless, we found only limited dosimetric differences due to inter-breath-hold uncertainties. Potentially, a more conformal treatment could be administered during breath-holding while organs at risk could be spared more adequately. As discussed in chapter 2, an optimal cut-off point between treatment robustness and conformity should be investigated in order to increase the potential benefit of scanned proton therapy.

Robustness of IMPT PBS-PT treatment to breath-hold uncertainties also depends to some extent on the beam angle selection. Gorgisyan et al. [8] recently investigated this aspect and found slightly higher water equivalent path length differences for lateral and posterior/anterior oblique beam angles. This was also observed by Chang et al. for free breathing 4DCT data [9]. The largest differences in water equivalent path length differences were explained by weight loss, tumour shrinkage, breath-hold reproducibility (lung volume changes) and baseline shifts of the tumour volume. Apparently, the lateral and posterior/anterior oblique beam angles were less robust to these type of changes. Clinically, patient specific choices that are also based on the tumour size and position as well as the position of organs at risk need to be made in order to choose the optimal beam angles.

Active motion mitigation by breath-hold increases the delivery time. Interruptions between breath-holds and additional time for patient setup prolong the treatment duration. Therefore, a limited number of breath-holds is preferred to deliver one fraction of radiotherapy treatment. Gorgisyan et al. [2] found that,

for most patients, up to three breath-holds were required for each field. This was the case for tumour volumes of 200 cm³ or less. In chapter 2, smaller tumour volumes (≤ 40 cm³) were included that required only one or two breath-holds per field. Consequently, a maximum of 10 breath-holds during each fraction are needed for a three-field plan and including a breath-hold CBCT scan during patient setup.

Breath-holding for 20 seconds per time can be easy to execute for many patients, but for some this may be very difficult and stressful [2, 10–13]. This can be due to a reduced lung capacity, but also psychological reasons may play a role (e.g. anxiety). Clear instructions, room for practice and visual guidance contribute to improve the compliance of patients and breath-hold execution [14–16]. Furthermore, it is important to consider the added value of breath-hold devices such as ABC, which may improve reproducibility, but may also be considered uncomfortable and consequently decrease patients compliance [1, 16]. Nevertheless, many studies have looked into this and found that, in general, breath-hold shows good compliance for repeated breath-holds of up to 20-25 seconds [2, 10, 11, 15, 16]. This has also been the threshold for the breath-hold duration in our study that is presented in chapter 2.

Looking at the benefits of breath-hold treatment, the breath-hold method is a relatively easy motion mitigation technique to implement in the clinic. Breath-holding mitigates the respiratory motion to a great extent, offering a quasi-static situation when executed perfectly [2]. A more conformal treatment compared to free breathing IMPT treatment can potentially be given, as we found limited intra- and inter-fraction breath-hold reproducibility uncertainties. Moreover, inspiration breath-hold results in an expanded lung volume and subsequently in a decreased irradiated lung volume during treatment [14, 17]. This reduces the risk of developing radiation pneumonitis [18]. Inspiration breath-hold also moves the heart inferiorly and this effect can be exploited when the target volume is located close to the cardiac region [17, 19–21].

In conclusion, our and other studies have shown that active motion man-

agement through breath-holding is feasible and from a clinical point of view a beneficial option for scanned proton treatments [2, 7]. Targets presenting motion amplitudes of more than 5 mm might already benefit. In chapter 3 we observed that for NSCLC patients, the targets moving 5 mm in amplitude will likely continue to exhibit motion in the range of 5 - 10 mm during the treatment course. Even for targets showing smaller motion amplitudes, about one third will move beyond 5 mm. However, the benefit in conformity and robustness of treatment comparing breath-hold versus free breathing treatments might only be clinically relevant for motion beyond 1 cm or even 1.5 cm. Future research should focus on the possible dosimetric benefits, but also on the robustness and efficiency of breath-hold versus free breathing IMPT PBS-PT treatment for different motion characteristics.

Inter-fraction target motion variations for NSCLC patients

Chapter 3 focused on free breathing PBS-PT treatment for NSCLC patients. Inter-fraction target motion variations were studied for a relatively large study population. Based on our own findings and those reported by other, we discussed a number of strategies needed for motion monitoring during free breathing PBS-PT. Target motion variations were measured through weekly 4DCTs and daily 4DCBCT imaging, by calculating the target centroid amplitudes of motion.

Recently, Steiner et al. [22] reported for lung stereotactic ablative radiotherapy patients that the amplitude motion as measured by these imaging modalities systematically underestimated the real target motion during treatment. These lung stereotactic ablative radiotherapy patients were considered to be highly mobile targets, which is not the case for about two-thirds of the locally advanced NSCLC patients that were included in our study population. However, it should be noted that breathing motion can vary during treatment due to target drifts, frequency changes and amplitude variations [22, 23]. All these types of variation are not fully captured during 4DCT or 4DCBCT imaging, and thus result in an underestimation of the target motion. The magnitude of these motion variations varies widely among patients, as reported by Steiner et al. [22]. In chapter 3 we observed

that the extreme target motion phases as captured during 4DCT imaging, were often in other than the extreme inhalation and exhalation 4DCT phases. This may be explained by the fact that the phases of the 4DCT are reconstructed based on an external motion surrogate, mostly the diaphragm region. Park et al. showed through dynamic MR imaging that a phase difference may exist between the surrogate respiratory signal and the actual target motion [24]. A careful selection of the extreme target motion phases during 4D robust optimization is therefore advised, especially because the 4DCT and 4DCBCT are likely to show already an underestimation of the motion due to breathing irregularities. In addition to daily imaging data that was used to determine the inter-fraction target motion variations, 4DCBCT scans were also acquired twice a week directly after treatment. The centroid motion amplitudes pre- and post-treatment fraction were calculated for these 4DCBCTs and evaluated for each patient (Fig. 1). For the nine patients that were evaluated, we found that 81% of the intra-fraction target motion amplitude differences remained less than 1 mm. Furthermore, 68% of the measurements depicted a decrease in motion amplitude. The largest intra-fraction motion differences were found for patient 3, 8 and 9. They showed a decrease in motion amplitude of maximally 5 mm and an increase in motion amplitude of no more than 3 mm. This indicates that free breathing treatment for advanced stage NSCLC is stable in gross tumour volume motion amplitude within one PBS-PT treatment fraction.

Figure 1. GTV centroid motion amplitudes from pre-treatment fraction and post-treatment fraction 4DCBCTs for nine patients. Patient data are presented in ascending order of motion amplitude.

Where breathing motion variations are evident, the dosimetric consequences can only be partly estimated and evaluated. In chapter 3 we showed one exemplary dosimetric evaluation for inter-fraction motion variations based on weekly 4DCT images. This research should be extended in future work to multiple cases to get a better idea of possible effects of intra-fraction amplitude motion on the proton dose distribution. Moreover, daily motion assessment with dosimetric evaluations should be performed, using for example daily 4DCBCT imaging in combination with techniques such as the creation of synthetic 4DCTs for proton dose recalculations.

4DCBCT from sparse-view data for daily motion monitoring during PBS-PT treatment

In chapter 4 the feasibility to reconstruct 4DCBCT scans from sparse-view data was investigated, which could provide an option for daily motion monitoring during PBS-PT treatment of moving targets. We have shown that the Motion-Aware RecOnstructiOn using Spatial and Temporal Regularization (MA-ROOSTER) method is a feasible method to create 4DCBCT images of sufficient image quality and assess the target motion in lung cancer patients. The published work is a first step towards implementing daily 4DCBCT imaging in proton therapy clinical practice.

The reconstruction workflow used for the research in chapter 4 is a semi-automatic workflow, where the Amsterdam Shroud method was applied during the phase binning process to select maxima and minima from the extracted respiratory signal [25, 26]. The internal respiratory signal was obtained from the projection data at a manually selected region, which is preferably the notably moving diaphragm region. However, the diaphragm may be obscured in some cases by the heart and by the limited projection image quality. Consequently, the diaphragm region does not present itself as a clearly visible periodic signal in the 2D Amsterdam Shroud image. Automatic selection and extraction of the breathing signal from the Amsterdam Shroud image is therefore a challenge. That is why, in most cases, we preferred to manually check and adjust the

selection and extraction of the breathing signal. Another option to improve the phase binning process could be to retrieve the respiratory signal externally. This could, for example, be done using the Anzai belt that is also used for respiratory gating during 4DCT acquisitions. We have investigated whether this would simplify and improve the phase binning process, compared to the internal respiratory signal provided by the Amsterdam Shroud method. For this research project, two sets of CBCT-projections and Anzai signals were acquired at the Groningen proton therapy centre for a porcine lung phantom that was available from the Ludwig-Maximilian University in Munich. For each set, three 4DCBCT images were reconstructed applying the MA-ROOSTER method, and projection binning was performed using the (A) Anzai signal and the Amsterdam Shroud method ([B] automatically and [C] manually corrected). A visual inspection of the reconstructed 4DCBCT images was performed at the diaphragm region. The structural similarity index measure values were calculated comparing the 4DCBCT quality to the 3DCBCT image quality. Results showed that the image quality of the 4DCBCT images was better for the Anzai belt signal method (A, Fig. 2). This phase binning method can be performed without manual intervention and is therefore the preferred approach for clinical 4DCBCT reconstruction at the Groningen proton therapy centre.

Table 1. Quality measure results for the reconstructed 4DCBCT scans for the three projection binning methods. The average structural similarity index measure values of the ten phases plus standard deviations are noted.

	A	B	C
	<i>SSIM (mean + SD)</i>		
4DCBCT 1	0.49 0.02	0.46 0.02	0.45 0.01
4DCBCT 2	0.49 0.02	0.45 0.01	0.44 0.01

Abbreviations: SSIM = structural similarity index measure (1 represents identical images, 0 represents completely non-identical images), A = Anzai method, B = Amsterdam Shroud, C = Amsterdam Shroud corrected.

	A	B	C
0% phase	SSIM: 0.51	SSIM: 0.43	SSIM: 0.46
50% phase	SSIM: 0.49	SSIM: 0.43	SSIM: 0.43

Figure 2. Coronal views with quality measure results for one of the 4DCBCTs (0% and 50% phases). The reconstructed diaphragms are compared for Amsterdam Shroud (A) and Anzai signal projection binning methods (B and C).

A recently published study by Bondesson et al. [27] extended the MA-ROOSTER workflow to create 4D virtual CT (4DvCT) scans using the planning 4DCT and CBCT projection data acquired at the Groningen proton therapy centre. They reconstructed the 4DCBCTs and applied the diffeomorphic morphons algorithm implemented in REGGUI by Janssens et al. [28] to calculate the velocity fields. The velocity fields were used to create the 4DvCT phases from the mid-ventilation 4DCBCT. These 4DvCTs were subsequently used for proton dose recalculations and the dose distributions were compared to the planning 4DCT doses. They investigated this workflow for the ex-vivo porcine lung phantom from the Ludwig-Maximilian University with known and reproducible breathing motion. Discrepancies between the 4DvCT and planning 4DCT were mainly found at the sliding diaphragm boundaries and steep tissue density gradients (Fig. 3). Gamma pass rates were above 96.7% and proton therapy treatment plan recalculations showed only minor (within 0.2%) differences in doses for the evaluated parameters (Table 2).

Figure 3. (1st to 3rd row) Display of sagittal slices from 4DCT as well as reconstructed 4DCBCT and 4DvCT images (ventilation phases 2, 4, 6, 8 and 10). Dotted lines highlight the diaphragm position at maximum exhale. The internal target volume is depicted in yellow. (4th row) Sagittal slices of difference images (4DvCT minus 4DCT) in Hounsfield Units. Red arrows highlight particular registration discrepancies occurring particularly around transitional points between tissue and the phantom. The black arrow highlights a vertical registration discrepancy at the same height as streaking artefacts produced in the CBCT reconstructions (adapted from Bondesson et al. [27]).

Table 2. (2nd to 4th column) Differences ($(CT-vCT)/CT$) in and between dose calculations on 4DCT and 4DvCT for the internal target volume (ITV). (5th column) Differences between dose calculations on 4DCT and 4D-vCT for the lungs (without the ITV). Values are displayed for all ventilation phases as well as for the accumulated dose from all 10 phases (adapted from Bondesson et al. [27]).

	$\Delta D_{2\%} \text{ (ITV) [\%]}$	$\Delta D_{95\%} \text{ (ITV) [\%]}$	$\Delta D_{98\%} \text{ (ITV) [\%]}$	$\Delta D_{\text{mean}} \text{ (ITV) [\%]}$	$\Delta D_{\text{mean}} \text{ (Lungs) [\%]}$
Phase 1	0.4	0.1	0.2	0.3	-0.4
Phase 2	0.1	0.3	0.7	0.1	5.1
Phase 3	-0.1	-0.2	-0.3	-0.2	5.5
Phase 4	-0.1	-0.7	-0.9	-0.3	5.8
Phase 5	-0.1	0.6	1.1	-0.1	5.1
Phase 6	-0.2	1.5	2.3	0.1	4.3
Phase 7	-0.1	0.7	1.2	0.1	3.2
Phase 8	0.1	-2.8	-4.9	-0.3	-5.4
Phase 9	0.1	0.1	0.0	0.1	1.1
Phase 10	0.5	-3.5	-5.7	-0.5	1.5
Accumulated	-0.0	-0.2	-0.1	-0.1	2.3

This proof of principle study showed that DIR-based 4DvCTs might be a feasible option for proton dose recalculations and possibly an adaptive proton therapy workflow. Of note that the current workflow takes 50 minutes to execute and can therefore only be used offline. Furthermore, future work is advised that involves clinical patient data with varying target and respiratory motion, and including realistic anatomical variations. Under these circumstances the feasibility and accuracy of a DIR-based 4DvCT proton dose recalculation workflow should be confirmed. Besides using DIR, a deep convolutional neural network can be trained and used to create 4DvCTs. At our institute, Thummerer et al. [29] investigated this method and compared it to a DIR method with the same algorithm as used by Bondesson et al. [27] and an analytical image-based correction method (AIC) method in 3D for head and neck cancer patients. They found that the image quality was best for the deep convolutional neural network. Dosimetrically, both the deep convolutional neural network and DIR method performed equally well [29]. In the presence of larger intra-fraction motion, a scatter correction method that uses the virtual CT as prior could result in improved CBCT image quality. This method has been investigated for 3D vCTs by Kurz et al. [30], where they compared the DIR-based vCTs to the CBCTs that were scatter corrected for head and neck cancer and prostate cancer patients. Currently, research is ongoing by the same research group in collaboration with UMCG to extend this method to 4DCBCTs of lung cancer patients and using the MA-ROOSTER reconstruction method.

Diaphragm based position verification to improve daily target dose coverage

The research that is presented in chapter 5 showed that a simple check with correction of the diaphragm position during pre-treatment CBCT imaging can improve the daily alignment of the target position. An additional shift during position verification effectively reduces major beam path density changes due to diaphragm offset changes. This should either reduce the need for re-planning or otherwise limit the dosimetric impact while waiting for a treatment plan adaptation. We found that this strategy is of added benefit for larger diaphragm deviations of more than 12 mm. This is because other applied robustness strategies,

such as robust optimization and choosing beam angles that are more robust to diaphragm position deviations, create treatments that are only robust to small and moderate diaphragm deviations [31].

Another recent publication from our institute from Roos et al. [32] also showed the importance of monitoring the diaphragm position offset. They did not find significant amplitude variations for the included patients, but observed larger offset changes resulting in dose deviations. Fig. 4 shows the difference in dose deviations between large and small offset changes for two example patients. Both the volumetric modulated arc therapy and IMPT treatment plans showed lack of treatment robustness to the larger diaphragm offset.

Figure 4. Dose distribution comparison of a volumetric modulated arc therapy plan with an IMPT plan of a patient with a large diaphragm position off-set (A) and a patient with a small diaphragm position off-set (B). For the volumetric modulated arc therapy plan, the planning target volume (dark red) and internal target volume (red) are shown and for the IMPT plan only the internal target volume (red) is shown (adapted from Roos et al. [32]).

In addition to 3D robust optimization and a robust beam angle choice, Visser et al. (manuscript conditionally accepted for publication) investigated the potential of a diaphragm density override technique during treatment planning to improve the proton treatment plan robustness. This technique has been successfully implemented in photon and proton treatments and is not as time-intensive compared to 4D robust optimization. However, they were not able to show the added

benefit of this technique to improve the robustness of scanned proton treatments to diaphragm position changes. This can be explained by the fact that the treatment plans were already found to be robust for most patients through the 3D robust optimization technique. The same lack of benefit was observed for 4D robust optimization for these patients. However, other research groups did find an added value for 4D robust optimization [33, 34]. Further research is therefore required to determine when exactly 4D robust optimization could be beneficial for the target coverage, especially as the computation time is expected to improve in the coming years, making this technique less time-intensive.

Diaphragm position variations are not the only factor influencing the target coverage during the treatment course. Other inter-fractional anatomical variations such as gastric filling, pleural effusion, bowel filling and mediastinal deformations can have a negative influence on the dose deposition. This is why repeated imaging remains important to monitor these changes, such as weekly 4DCT and daily 4DCBCT imaging.

Future perspectives

Further steps can be taken to support and improve the clinical implementation of IMPT PBS-PT treatment for moving targets. For active motion mitigation using breath-holding, repeated imaging before start of treatment and inter-fractional daily breath-hold imaging can provide helpful information about the patient specific reproducibility. A recommendation would be to perform this for the first group of patients that is treated in breath-hold with IMPT PBS-PT. These images can then be used to evaluate the robustness of the treatment plans to these different breath-hold geometries. For free breathing treatment of moving targets (e.g. tumours moving more than 2 mm in motion amplitude) daily motion monitoring is recommended. Future work could include actual NSCLC patients treated during free breathing that receive daily 4DCBCT imaging, where the 4DCBCT images will be used to evaluate the fractional proton dose distributions (for example using a virtual 4DCT approach). Based on the observed trends, the robustness approaches can be evaluated for patients individually and plan adaptation deci-

sions can be made accordingly if necessary. We have already shown in chapter 4 the feasibility of a 4DCBCT reconstruction workflow for sparse-view data. Future work would be to confirm this finding for our own patient population and for the CBCT data acquired at the Proteus©Plus gantry (IBA, Louvain-la-Neuve, Belgium). Next steps would then be to fully automatize and ultimately to implement the 4DCBCT reconstruction workflow for clinical use. Other future work could be to investigate which patients would be best treated during free breathing and for which patients active motion monitoring during breath-holding should be recommended. It would be interesting to investigate the two options for the same patient population. This would require a study where repeated breath-hold imaging is performed in addition to the free breathing treatment. A treatment plan comparison could be done with different robustness strategies, together with a robustness evaluation based on the repeated breath-hold images acquired during the course of treatment. If a clinically relevant benefit were found for breath-hold treatments for a certain patient group and/or motion characteristics, then this should be weighed against other factors: for example, the increase in delivery time. I expect that only for big movers (motion amplitudes beyond 1 cm) active motion mitigation is beneficial. The diaphragm position check and correction method during position verification has recently been clinically implemented. Evaluation of how often the correction is necessary and beneficial is ongoing. Future studies could examine an optimal threshold value of the diaphragm position deviation to help decide when to apply the correction. Following our research, this could be a deviation of 12 mm of the diaphragm position, although this might become a different threshold value when this method has been evaluated for a larger patient population. Overall, this research aims to improve PBS-PT treatments for moving targets and facilitate clinical introduction of the IMPT in hemithorax.

References

1. Kaza E, Dunlop A, Panek R, et al. Lung volume reproducibility under ABC control and self-sustained breath-holding. *J Appl Clin Med Phys* 2017;18:154–62.

2. Gorgisyan J, Munck af Rosenschold P, Perrin R, et al. Feasibility of pencil beam scanned intensity modulated proton therapy in breath-hold for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017;99:1121–8.
3. Scherman Rydhög J, Riisgaard de Blanck S, Josipovic M, et al. Target position uncertainty during visually guided deep-inspiration breath-hold radiotherapy in locally advanced lung cancer. 2017.
4. Gorgisyan J, Lomax AJ, Rosenschold PM af, et al. The dosimetric effect of residual breath-hold motion in pencil beam scanned proton therapy An experimental study. 2019.
5. Bernatowicz K, Lomax AJ, and Knopf A. Comparative study of layered and volumetric rescanning for different scanning speeds of proton beam in liver patients. *Phys Med Biol* 2013;58:7905–20.
6. Zhang Y, Knopf AC, Weber DC, and Lomax AJ. Improving 4D plan quality for PBS-based liver tumour treatments by combining online image guided beam gating with rescanning. *Phys Med Biol* 2015;60:8141–59.
7. 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. *Int J Radiat Oncol Biol Phys* 2017;99:41–50.
8. Gorgisyan J, Perrin R, Lomax AJ, et al. Impact of beam angle choice on pencil beam scanning breath-hold proton therapy for lung lesions. *Acta Oncol* 2017;56:853–9.
9. Chang JY, Li H, Zhu XR, et al. Clinical implementation of intensity modulated proton therapy for thoracic malignancies. *Int J Radiat Oncol Biol Phys* 2014;90:809–18.
10. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874–900.
11. Panakis N, McNair HA, Christian JA, et al. Defining the margins in the radical radiotherapy of non-small cell lung cancer (NSCLC) with active breathing control (ABC) and the effect of physical lung parameters. *Radiother Oncol* 2008;65–73.
12. Persson G, Aznar M, Rydhög J, et al. Deep Inspiration Breath Hold Compliance in Radiation Therapy for Locally Advanced Lung Cancer. In: *International Journal of Radiation Oncology*Biology*Physics*. Vol. 99. 2. 2017:E491.
13. Chander A, Iqbal J, and Needleman S. Deep Inspiratory Breath Hold Technique to Reduce Cardiotoxicity when Delivering Left Breast.pdf. In: *Clin Oncol* 31. London, UK, 2019:e103–e116.

14. 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;94:478–92.
15. Sarrut D, Boldea V, Ayadi M, et al. Nonrigid registration method to assess reproducibility of breath-holding with ABC in lung cancer. *Int J Radiat Oncol Biol Phys* 2005;61:594–607.
16. McNair HA, Brock J, Symonds-Tayler JRN, et al. Feasibility of the use of the Active Breathing Coordinator (ABC) in patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC). *Radiother Oncol* 2009;93:424–9.
17. Remouchamps VM, Vicini FA, Sharpe MB, Kestin LL, Martinez AA, and Wong JW. Significant reductions in heart and lung doses using deep inspiration breath hold with active breathing control and intensity-modulated radiation therapy for patients treated with locoregional breast irradiation. *Int J Radiat Oncol Biol Phys* 2003;55:392–406.
18. Marks L, Bentzen S, Deasy J, et al. Radiation Dose-Volume Effects. *Int J Radiat Oncol Biol Phys* 2010;76:S70–S76.
19. Dabaja BS, Hoppe BS, Plataras JP, et al. Proton therapy for adults with mediastinal lymphomas: The international lymphoma radiation oncology group guidelines. *Blood* 2018;132:1635–46.
20. Hoppe BS, Mendenhall NP, Louis D, Li Z, and Flampouri S. Comparing Breath Hold and Free Breathing during Intensity-Modulated Radiation Therapy and Proton Therapy in Patients with Mediastinal Hodgkin Lymphoma. *Int J Part Ther* 2017;3:492–6.
21. Everett AS, Hoppe BS, Louis D, et al. Comparison of Techniques for Involved-Site Radiation Therapy in Patients With Lower Mediastinal Lymphoma. 2019.
22. Steiner E, Shieh CC, Caillet V, et al. Both four-dimensional computed tomography and four-dimensional cone beam computed tomography under-predict lung target motion during radiotherapy. *Radiother Oncol* 2019;135:65–73.
23. Seppenwoolde Y, Shirato H, Kitamura K, et al. Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. *Int J Radiat Oncol Biol Phys* 2002;53:822–34.
24. Park S, Farah R, Shea SM, Tryggestad E, Hales R, and Lee J. Simultaneous tumor and surrogate motion tracking with dynamic MRI for radiation therapy planning. *Physics in Medicine and Biology* 2018;63.

25. Zijp L, Sonke J, and Herk M van. Extraction of the respiratory signal from sequential thorax cone-beam X-ray images. In: *Proceedings of the 14th ICCR*. Seoul, Korea, 2004:507–9.
26. Herk M van, Zijp L, Remeijer P, Wolthaus J, and Sonke J. On-line 4D cone beam CT for daily correction of lung tumour position during hypofractionated radiotherapy. In: *Proc 15th ICCR*. Toronto, Canada, 2007.
27. Bondesson D, Meijers A, Janssens G, et al. Anthropomorphic lung phantom based validation of in-room proton therapy 4D-CBCT image correction for dose calculation. *Z Med Phys* 2020;1–11.
28. Janssens G, Jacques L, Orban De Xivry J, Geets X, and MacQ B. Diffeomorphic registration of images with variable contrast enhancement. *Int J Biomed Imaging* 2011;1–16.
29. Thummerer A, Zaffino P, Meijers A, et al. Comparison of CBCT based synthetic CT methods suitable for proton dose calculations in adaptive proton therapy. *Physics in Medicine and Biology* 2020;65.
30. Kurz C, Kamp F, Park YK, et al. Investigating deformable image registration and scatter correction for CBCT-based dose calculation in adaptive IMPT. *Med Phys* 2016;43:5635–46.
31. Yu J, Zhang X, Liao L, et al. Motion-robust intensity-modulated proton therapy for distal esophageal cancer. *Med Phys* 2016;43:1111–8.
32. Roos CT, Faiz Z, Visser S, et al. A comprehensive motion analysis consequences for high precision image-guided radiotherapy of esophageal cancer patients. *Act Oncol* 2020;4–12.
33. Liu W, Schild SE, Chang JY, et al. Exploratory study of 4D versus 3D robust optimization in intensity-modulated proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 2017;95:523–33.
34. Ge S, Wang X, Liao Z, et al. Potential for improvements in robustness and optimality of intensity-modulated proton therapy for lung cancer with 4-dimensional robust optimization. *Cancers* 2019;11:35.

Chapter 7

Nederlandse samenvatting

Nederlandse samenvatting

Introductie

In Nederland worden jaarlijks meer dan 2.500 en 10.000 patiënten gediagnosticeerd met respectievelijk slokdarmkanker en (niet-kleincellige) longkanker (NSCLC). Radiotherapie is een belangrijk onderdeel van de behandeling van deze soorten kanker, vaak in combinatie met chirurgie of chemotherapie of aanvullend met immunotherapie. Bij radiotherapie wordt de tumor lokaal en met hoog energetische straling bestraald. Het primaire doel daarbij is de tumorcontrole en secundair is het doel om omringende gezonde weefsels en organen te sparen en daarmee de kans op complicaties zo klein mogelijk te houden. Sinds enkele jaren is ook protonentherapie mogelijk in Nederland. Protonen hebben de eigenschap dat ze de meeste energie afgeven aan het einde van hun pad en dan stoppen, volgens de zogeheten Bragg-piek (een piek van energieafgifte op de zogenoemde Bragg-curve). De locatie van de Bragg-piek is afhankelijk van de meegegeven hoge energie (tussen de 70 en 230 mega-elektronvolt) en de soorten weefsels die de protonen tegenkomen in het lichaam. De geavanceerde protonentherapie techniek die ook wordt toegepast in het protonentherapiecentrum van het universitair medisch centrum Groningen is de zogeheten pencil beam scanning protonentherapie (PBS-PT). PBS-PT maakt gebruik van zeer smalle protonenbundels die gericht worden door magneten en zo het te behandelen doelvolumen kunnen scannen. Een veelgebruikte moderne techniek voor bestralingsplanning daarbij is de intensiteitsgemoduleerde protonentherapie (intensity modulated proton therapy [IMPT]). IMPT PBS-PT is een zeer conforme bestralingstechniek die voor een aantal soorten kanker, waaronder slokdarmkanker en NSCLC, nog meer kan betekenen als het gaat om het sparen van kritieke organen. Wanneer de tumor echter beweegt (bijv. ademhaling) is het nauwkeurig bestralen daarentegen een uitdaging om te voorkomen dat er bijvoorbeeld heterogeniteiten ontstaan in de dosis distributie met te weinig dosis dan wel een overdosering van het doelvolumen en/of omringende kritieke organen. Daarom is het belangrijk om te kijken naar geschikte methodes om de bewegingen van de tumor en de omliggende structuren te monitoren tijdens de behandeling met PBS-PT. In deze thesis zijn een aantal aspecten die hiermee

te maken hebben onderzocht om zo een positieve bijdrage te leveren aan de implementatie van PBS-PT voor de behandeling van bewegende tumoren.

Reproduceerbaarheid van de longen bij gebruik van de active breathing coordinator (ABC)

Het is gebruikelijk binnen de radiotherapie om methodes toe te passen bij bewegende tumoren die de beweging beperken tijdens elke bestralingsfractie. Eén van de mogelijke technieken is breath-holding, waarbij de ademhaling bij inspiratie voor een korte periode (± 20 seconden) vastgehouden wordt. In hoofdstuk 2 is onderzoek gedaan naar de reproduceerbaarheid van een specifieke breath-hold techniek met behulp van een apparaat dat actief de ademhaling coördineert door de ingeademde hoeveelheid volume aan lucht te controleren (active breathing coordinator [ABC]). Aangetoond is namelijk in eerder gepubliceerd onderzoek dat het volume aan geïnspireerde lucht goed reproduceerbaar is. In hoofdstuk 2 werd aanvullend onderzocht of dit ook geldt voor de anatomie van de longen. Het is namelijk noodzakelijk voor de implementatie van PBS-PT om inzicht te hebben in de mogelijke positievariëaties van het doelvolumen tijdens een bestralingsfractie en tussen de bestralingsfracties. Deze onzekerheden kunnen dan meegenomen worden in het robuust plannen van de behandeling. Onze studie heeft bevestigd dat breath-holding met behulp van ABC-controle een reproduceerbare techniek is, met mediane longanatomie verplaatsingen van 1,6 mm inter-fractioneel en 1,3 mm intra-fractioneel. Daarnaast zijn de dosimetrische gevolgen onderzocht van deze verplaatsingen voor robuust geplande IMPT PBS-PT behandelplannen met een 5 mm setup marge en 3% range error. Daaruit kwam naar voren dat 22 van de 23 gesimuleerde breath-hold scenarios robuust waren voor de onzekerheden die voortkomen uit het herhalen van de breath-hold techniek (minimaal 95% van de voorgeschreven dosis [60 Gy] voor 98% van het doelvolumen). Bovendien was een toename in dosis voor het doelvolumen enkel gevonden tot een maximum van 110% van de voorgeschreven dosis. Tenslotte zijn minimale verschillen in dosis gevonden voor de organen die binnen het dosisgebied liggen. Dit betekent dat actieve bewegingsbeperking door middel van breath-holding uitvoerbaar en reproduceerbaar genoeg is om

gebruikt te worden voor PBS-PT.

Inter-fractionele bewegingsvariaties van het doelvolumen van NSCLC-patiënten

Bewegende tumoren kunnen ook worden bestraald tijdens een normale vrije ademhaling. Daarom is er onderzocht in hoofdstuk 3 wat de mate van beweging (bijv. amplitude) van longtumoren is onder invloed van (voornamelijk) de ademhaling en wat de variatie is van deze tumorbeweging gedurende de meerdere weken dat de protonentherapiebehandeling duurt. Verder werd in hoofdstuk 3 aandacht besteed aan het gebruik van wekelijkse 4D computertomografie (4DCT) beelden vergeleken met het mogelijk dagelijks beeldvormen met behulp van 4D cone beam CT beelden (4DCBCT). Bekeken werd of het nodig is om dagelijks te scannen en wat de meerwaarde daarvan zou zijn. Uit het onderzoek kwam naar voren dat de mediane amplitudebeweging voor de patiënten 3,4 mm was (range: 0,2 - 12,4 mm). Tien van de 32 patiënten (31,3%) die geïnccludeerd waren en initieel een tumorbeweging hadden van minder dan 5 mm, lieten een toename van de amplitudebeweging zien voorbij deze grens van 5 mm. De dagelijkse 4DCBCT beelden weken gemiddeld 1,5 mm (range: 0,0 - 6,0 mm) af van de beweging zoals gevonden was in de wekelijkse 4DCT beelden. Voor één voorbeeldpatiënt met een relatief grote bewegingsvariatie is vervolgens een IMPT PBS-PT plan gesimuleerd. Het gesimuleerde IMPT PBS-PT plan bleek niet robuust te zijn voor de geobserveerde grotere bewegingsvariaties. Uit dit onderzoek kan uiteindelijk geconcludeerd worden dat enkel amplitudebewegingen van 2 mm of minder daadwerkelijk stabiel blijven (≤ 5 mm) gedurende de weken van protonentherapiebehandeling. Voor de behandeling van NSCLC-patiënten die een beweging laten zien van meer dan 2 mm is het dagelijks beeldvormen van de tumorbeweging geadviseerd door middel van bijvoorbeeld 4DCBCT-beeldvorming.

4DCBCT van sparse-view data voor dagelijkse monitoring van de beweging van het tumorvolume tijdens PBS-PT behandeling

4DCBCT-reconstructies zijn nog niet klinisch beschikbaar voor protonentherapie in de gebruikte software, maar in 3D worden al wel CBCT-beelden gemaakt

voor dagelijkse positieverificatie vooraf aan elke bestralingsfractie. Daarom is in deze thesis onderzoek gedaan in hoofdstuk 4 naar een geschikte methode voor 4DCBCT reconstructies. Deze reconstructies moeten dan gemaakt kunnen worden van de beperkt aantal projecties die dagelijks verkregen worden om CBCT-scans te reconstrueren tijdens de positieverificatie. Dat zou namelijk het implementeren van 4DCBCT reconstructies vereenvoudigen, aangezien er geen extra lange scan gemaakt hoeft te worden met extra stralingsdosis en het bovendien ook niet de duur van de bestralingsfractie verlengt. Voor een goede kwaliteit van de 4DCBCT beelden zijn echter normaal gesproken een groot aantal projecties vereist. Deze projecties worden meestal opgedeeld in 8-10 groepen (bins). Deze bins worden apart gereconstrueerd en geven dan het in beeld gebrachte deel van het lichaam inclusief het doelvolumen weer in een verschillende fase van de ademhaling. Er is daarom een geavanceerde reconstructiemethode noodzakelijk die ook met een gelimiteerde hoeveelheid projecties 4DCBCT's kan reconstrueren van voldoende kwaliteit om die tumorbeweging dagelijks te kunnen kwantificeren. We hebben aangetoond in deze studie dat de zogeheten Motion-Aware ReconstructiOn using Spatial and Temporal Regularization (MA-ROOSTER) methode geschikt is om 4DCBCT beelden van voldoende beeldkwaliteit te maken om de (amplitude)beweging van het tumorvolume te evalueren voor longkankerpatiënten. De beeldkwaliteit voor de MA-ROOSTER 4DCBCT reconstructies bleek namelijk superieur te zijn aan die van de (phase-correlated [PC]) Feldkamp-Davis Kress (FDK) methode. Dit was gekwantificeerd met behulp van de contrast-to-noise ratio (CNR, mediaan: 1,23 [PC-FDK], 1,98 [MA-ROOSTER], 1,98 [FDK]), de signal-to-noise ratio (SNR, mediaan: 2,56 [PC-FDK], 4,76 [MA-ROOSTER], en 5,02 [FDK]) en de structural similarity index measure (SSIM, mediaan: 0,18 [PC-FDK vs. FDK], 0,31 [MA-ROOSTER vs. FDK]). Daarbij was het mogelijk om de tumorbeweging te kwantificeren aan de hand van de gereconstrueerde MA-ROOSTER 4DCBCT's. De workflow is momenteel nog semi-automatisch, maar er zijn mogelijkheden om dit volledig te automatiseren. Deze evaluatie was bovendien gedaan voor klinische data van patiënten die daadwerkelijk behandeld zijn met PBS-PT. Dit gepubliceerde werk draagt dan ook bij aan de mogelijke implementatie van

dagelijkse 4DCBCT-beeldvorming in de protonentherapie kliniek.

Diafragma-gebaseerde positieverificatie voor het verbeteren van de dagelijkse dosisdekking voor het doelvolumen

In hoofdstuk 5 wordt een aanvullende check met mogelijke correctie van de positie van het diafragma beschreven tijdens de dagelijkse positieverificatie van slokdarmkankerpatiënten. Dit om te monitoren of de positie van het diafragma voldoende reproduceerbaar is tussen de bestralingsfracties ten opzichte van de planningssituatie. Bij een grote afwijking is een adequate bestraling van het tumorvolume mogelijk in het geding vanwege de grote verandering in soorten weefsels die de protonenbundels tegenkomen in het lichaam. De geplande Bragg-pieken zullen dan op andere posities terechtkomen, met een onderdosering dan wel overdosering op plekken binnen en buiten het tumorvolume tot gevolg. Een correctie voor de grotere afwijkingen van het diafragma kan daarom onder andere de aanpassing van een bestralingsplan voorkomen en de uiteindelijke gegeven dosis aan het tumorvolume zoveel mogelijk volgens het oorspronkelijke plan houden. Is er ondanks de correctie een planadaptatie noodzakelijk, dan kan deze correctie alsnog als een tijdelijke tussenoplossing dienen. Metingen van de positie van het doelvolumen lieten namelijk zien dat de inter-fractionele verplaatsingen het grootst waren in de craniaal-caudale richting (range: -6,5 - 13,5 mm). De craniaal-caudale gemiddelde verplaatsingen ($r=0,838$), sub-maximale verplaatsingen (95-percentiel; $r=0,772$) en caudale grensverplaatsingen ($r=0,729$) van het doelvolumen correleerden met de verplaatsingen van het diafragma. De craniaal-caudale gemiddelde doelvolumeverplaatsing was congruent met bijna de helft van de diafragma verplaatsing ($y=0,439x$). De helft van de diafragmaverplaatsing was gebruikt voor de correctie bij de nieuwe positieverificatiemethode. Bij de evaluatie van de robuustheid van de dosisdistributies voor de diafragma positie variaties gebaseerd op de wekelijkse 4DCT's kwam naar voren dat de doelvolumedosering adequaat was voor de patiënten met diafragma positie verplaatsingen tot 12 mm ($\geq 94\%$ van de dosis in 98% van het volume). Voor de grotere diafragma positie verplaatsingen was de dosering voor het doelvolumen beter behouden bij gebruik van de positieverificatiemethodes gebaseerd op alleen het doelvolumen (PV_T) of

de methode gebaseerd op de botstructuren met aanvullende correctie van het diafragma (PV_BD). De PV_BD methode werkte het beste voor de verplaatsingen in combinatie met grote veranderingen in weefseldensiteit in het gebied rond het diafragma ($D_{98\%}$: IMPT $95\% \pm 5\%$, volumetric modulated arc therapy [VMAT] $97\% \pm 6\%$). Vergelijkbare incidentie en grootte van de inter-fractionele diafragma verplaatsingen was gevonden voor de wekelijkse 4DCT's en de dagelijkse 4DCBCT's. Een diafragmaverplaatsing van meer dan 12 mm was gevonden in 16% (4DCT's) en 20% (4DBCT's) van de gevallen. Intra-fractionele diafragmapositiemonitoring liet zien dat systematische afwijkingen standhielden gedurende een bestralingsfractie. Dit valideerde het nut en de noodzaak voor het gebruik van een correctiemethode tijdens positieverificatie op basis van de positie van het diafragma. Voor de meeste gevallen was de (conventionele) verificatiemethode gebaseerd op alleen de botstructuren (PV_B) methode wel voldoende om de minimaal benodigde dosis voor het doelvolumen te bereiken. Maar voor grote afwijkingen in positie van het diafragma bleek dat een aanvullende correctie volgens de PV_BD methode die afwijking kon beperken. Het dagelijks monitoren van de positie van het diafragma tijdens de behandeling vooraf aan de bestralingsfractie is daarom aanbevolen, om zo een betere dekking van de dosis te bereiken en een eventuele plan adaptatie te kunnen ondersteunen.

Toekomstperspectief

Verdere stappen kunnen genomen worden om de klinische implementatie van protonentherapie voor bewegende tumoren te ondersteunen en te verbeteren door het doen van aanvullend onderzoek. Naar aanleiding van hoofdstuk 2 zou bijvoorbeeld een studie gedaan kunnen worden voor de eerste groep van minimaal twintig patiënten die mogelijk in de toekomst protonentherapie krijgen gedurende breath-holding. Daarbij kan dan meermaals worden gescand in breath-hold vooraf aan de behandeling bij de planningssimulatie (4DCT's) en ook inter-fractioneel vooraf aan elke behandelingsfractie (4DCBCT's). Dit geeft dan een aardig beeld van de patiëntspecifieke reproduceerbaarheid van breath-holding voor de eigen patiëntenpopulatie. Bovendien kunnen de 4DCBCT's gebruikt worden om de robuustheid van de behandeling te evalueren

aan de hand van de verschillende breath-hold geometrieën. Voor protonentherapiebehandeling met vrij doorademen voor bewegende tumoren die meer dan 2 mm bewegen in amplitude (hoofdstuk 3), is het aanbevolen om dagelijks de tumorbeweging te monitoren. Toekomstig onderzoek kan gebruik maken van deze bewegingsdata, van bijvoorbeeld longkankerpatiënten, door de dagelijkse en gesommeerde dosisdistributies te evalueren (bijvoorbeeld m.b.v. de virtuele 4DCT methode). Gebaseerd op de gevonden trends in tumorbeweging en de dosimetrische gevolgen die gevonden zijn, kunnen de robuustheidsmethodes die gebruikt zijn tijdens de planning van de behandeling geëvalueerd worden op hun effectiviteit. Een beslissing voor een eventuele planadaptatie zou bovendien beter geïnformeerd genomen kunnen worden in vergelijking met enkel wekelijks scannen m.b.v. 4DCT beeldvorming. In hoofdstuk 4 is aangetoond dat er een geschikte 4DCBCT reconstructiemethode is voor het reconstrueren met slechts een beperkt aantal projecties. Toekomstig onderzoek zou kunnen gaan over het bevestigen van deze bevindingen voor eigen CBCT data van het Groningen protonentherapiecentrum. Aanvullende stappen zijn dan om de workflow volledig te automatiseren en ook klinisch te implementeren. Ander toekomstig onderzoek kan zich richten op de vraag welke patiënten geschikt zijn voor behandeling tijdens vrij doorademen en welke patiënten beter gedurende breath-hold behandeld kunnen worden. Het meest interessant is om een vergelijking te maken binnen dezelfde patiëntenpopulatie. Dit zou wel vereisen dat er meerdere keren gescand wordt in zowel breath-holding als tijdens vrij doorademen. Behandelplannen voor protonentherapie tijdens vrij ademen en tijdens breath-holding kunnen dan vergeleken worden met mogelijk verschillende robuustheidsstrategieën en met een robuustheidsevaluatie gebaseerd op de herhaalde (4DCT/4DCBCT) beelden tijdens de behandeling. Gekeken kan worden of er dan een klinisch relevant voordeel is voor protonentherapiebehandeling tijdens breath-hold voor een specifieke groep patiënten of specifieke tumorbewegingen. Dit moet dan wel afgewogen worden tegen eventuele andere nadelen, zoals de toename in behandeltime. Ik verwacht dat alleen bewegende tumoren met een amplitude van meer dan 1 cm in aanmerking komen voor breath-hold behandeling. Het monitoren de positie van het diafragma met een

aanvullende correctie is recent in de kliniek ingevoerd en er wordt bekeken hoe vaak deze correctie nodig blijkt te zijn. Toekomstig onderzoek zou kunnen gaan over het bepalen van een geschikte drempelwaarde van de afwijking van de positie van het diafragma, die gebruikt kan worden om te beslissen of een correctie moet worden toegepast of niet. De voorlopige drempelwaarde is 8 mm met een correctie tot maximaal 6 mm, maar dit zou aangepast kunnen worden aan de hand de evaluatie voor de grotere groep patiënten die ondertussen behandeld is en waarvoor deze methode is toegepast.

Concluderend, het doel is om bij te dragen aan een verbeterde en veilige behandeling van bewegende tumoren met protonentherapie. Dit kan dankzij het onderzoek dat is en wordt gedaan binnen het Groningen protonentherapiecentrum en universitair medisch centrum Groningen. Uiteindelijk is het dan ook het doel voor de nabije toekomst om protonentherapie toegankelijk te maken voor alle bewegende tumoren.

Appendices

Dankwoord

Dankwoord

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Curriculum Vitae

Curriculum Vitae

Lydia Anneke den Otter was born on Januari 10th 1991 in Zeist, the Netherlands. After finishing high school in 2009 in Groningen, she went to Enschede to study Technical Medicine. She obtained her bachelor's degree in 2012. The bachelor research project was entitled "Inter- en intrafractional tracking and tracing with magnetic nanoparticles: clinical implementation". With this project her interest in radiotherapy treatments began. She obtained her masters' degree of Technical Medicine specialized in 'Medical Imaging and Interventions' in 2016 at the 'radiothera-

piegroep' in Deventer, with the final research project entitled "Introduction of volumetric modulated arc therapy (VMAT) for the treatment of left-sided breast cancer and internal mammary nodes for the Elekta linear accelerator". Then she moved back to Groningen and started her PhD project at the Radiation Oncology department of the University Medical Center in Groningen under supervision of dr. Antje-Christin Knopf and Prof. dr. Hans Langendijk. In the following years she worked on several international projects that were related to the clinical introduction of proton therapy treatment for moving targets and so this PhD thesis was born. At this very moment, she is broadening her working experience by working as a humanitarian aid coordinator at the Netherlands Red Cross.

List of publications

List of publications

Journal articles

1. Kierkels RGJ, **den Otter LA**, Korevaar EW, Langendijk JA, van der Schaaf A, Knopf A-C, Sijtsema NM. *An automated, quantitative, and case-specific evaluation of deformable image registration in computed tomography images*. Phys Med Biol 2018;63(4):045026
2. Schröder FF, Huis in't Veld R, **den Otter LA**, van Raak SM, ten Haken B, Vochteloo AJH. *Metal artefacts severely hamper magnetic resonance imaging of the rotator cuff tendons after rotator cuff repair with titanium suture anchors*. Shoulder Elbow 2018;10(2):107-113
3. **den Otter LA**, Kaza E, Kierkels RGJ, Meijers A, Ubbels JF, Leach MO, Collins DJ, Langendijk JA, Knopf A-C. *Reproducibility of the lung anatomy under active breathing coordinator control: Dosimetric consequences for scanned proton treatments*. Med Phys 2018;45(12):5525-5534
4. **den Otter LA**, Anakotta RM, Weessies M, Roos CTG, Sijtsema NM, Muijs CT, Dieters M, Wijsman R, Troost EGC, Richter C, Meijers A, Langendijk JA, Both S, Knopf A-C. *Investigation of inter-fraction target motion variations in the context of pencil beam scanned proton therapy in non-small cell lung cancer patients*. Med Phys 2020;47(9):3835-3844
5. Bondesson D, Meijers A, Janssens G, Rit S, Rabe M, Kamp F, Niepel K, **den Otter LA**, Both S, Brousmiche S, Dinkel J, Belka C, Parodi K, Knopf A-C, Kurz C*, Landry G*. *Anthropomorphic lung phantom based validation of in-room proton therapy 4D-CBCT image correction for dose calculation*. Z Med Phys Nov 2020
6. Roos, CTG, Faiz Z, Visser S, Dieters M, van der Laan HP, **den Otter LA**, Plukker JTM, Langendijk JA, Knopf A-C, Muijs CT, Sijtsema NM. *A comprehensive motion analysis - consequences for high precision image guided radiotherapy of esophageal cancer patients*. Acta Oncol Nov 2020

7. **den Otter LA**, Chen K, Janssens G, Meijers A, Both S, Langendijk JA, Rosen LR, Wu HT, Knopf A-C. *Technical note: 4D cone-beam CT reconstruction from sparse-view CBCT data for daily motion assessment in pencil beam scanned proton therapy (PBS-PT)*. Med Phys 2020;47(12):6381-6387
8. Visser S*, **den Otter LA***, Ribeiro CO, Korevaar EW, Both S, Langendijk JA, Muijs CT, Sijtsema NM, Knopf A-C. *Diaphragm based position verification to improve daily target dose coverage in proton and photon radiotherapy treatment of distal esophageal cancer*. Int J Radiat Oncol Biol Phys 2021
*contributed equally

Grants

1. ESTRO Mobility Grant (March, 2018). *4DCBCT reconstruction for moving targets for scanned proton therapy*. Willis Knighton Cancer Center, Shreveport LA, USA.
2. 4D Treatment Workshop for Particle Therapy - Travel Grant (December, 2018). *First steps towards a 4D cone-beam CT reconstruction workflow for moving targets at a scanned proton gantry system*. Hokkaido University, Sapporo, Japan.

Accepted abstracts for international conferences

1. Oral presentation. ESTRO 2016 (Turin, Italy). *A simple visual test is adequate for testing vmDIBH reproducibility in locoregional breast cancer*. den Otter LA, Nuver TT, Boerhof M, Kolkman-Nijland HH, Schoevers WJ, Muller K, Minken AWH.
2. Oral presentation. ESTRO 2017 (Vienna, Austria). *Evaluation of lung anatomy vs. volume reproducibility for scanned proton treatments under Active Breathing Control*. den Otter LA, Kaza E, Kierkels RGJ, Leach MO, Collins DJ, Langendijk JA, Knopf A-C.
3. Poster. PTCOG 2017 (Yokohama, Kanagawa, Japan). *Reproducibility of the lung anatomy using Active Breathing Control: Dosimetric consequences*

- for scanned proton treatments.* den Otter LA, Kierkels RGJ, Kaza E, Meijers A, Leach MO, Collins DJ, Langendijk JA, Knopf A-C.
4. Poster. 4D Treatment Workshop for Particle Therapy 2017 (Vienna, Austria). *Reproducibility of the lung anatomy under Active Breathing Coordinator control: Dosimetric consequences for scanned proton treatments.* den Otter LA, Kaza E, Kierkels RGJ, Meijers A, Ubbels JF, Leach MO, Collins DJ, Langendijk JA, Knopf A-C.
 5. Poster. ESTRO 2018 (Barcelona, Spain). *Treating moving targets with scanned proton therapy: Is 5 mm initial tumour motion a safe threshold?* den Otter LA, Anakotta RM, Dieters M, Muijs CT, Both S, Knopf A-C.
 6. Poster. PTCOG 2018 (Cincinnati, USA). *The necessity of 4D-motion monitoring for thoracic tumors treated with pencil beam scanning proton therapy: a comprehensive 4D-imaging study.* den Otter LA, Anakotta RM, Dieters M, Muijs CT, Both S, Langendijk JA, Knopf A-C.
 7. Poster. 4D Treatment Workshop for Particle Therapy 2018 (Sapporo, Japan). *First steps towards a 4D Cone-beam CT reconstruction workflow for moving targets at a scanned proton gantry system.* den Otter LA, Chen K, Janssens G, Meijers A, Both S, Langendijk JA, Wu HT, Knopf A-C.
 8. Poster. ESTRO 2019 (Milan, Italy). *Investigating 4DCBCT reconstruction for moving targets at a scanned proton gantry system.* den Otter LA, Chen K, Janssens G, Meijers A, Both S, Langendijk JA, Rosen LR, Wu HT, Knopf A-C.
 9. Poster. PTCOG 2019 (Manchester, UK). *Optimization of 4DCBCT image reconstruction at proton gantry systems.* den Otter LA, Kurz C, Stanislawski M, Parodi K, Landry G, Janssens G, Meijers A, Both S, Langendijk JA, Knopf A-C.
 10. Oral presentation. ESTRO 2021 (Madrid, Spain) *Improved robustness in oesophageal cancer treatment by diaphragm based position verification.* Visser S*, den Otter LA*, Ribeiro CO, Korevaar EW, Both S, Langendijk JA, Muijs CT, Sijtsma NM*, Knopf A-C*. *contributed equally