1 Discussion

This is a first in silico study directly comparing clinical stereotactic body radiation therapy (SBRT) with scanned carbon-ions (PT) for non-small cell lung cancer (NSCLC). Our results show that PT could be considered an alternative to SBRT, with the same tumor coverage and less dose to OARs. Furthermore, the study was expanded to patients with multiple NSCLC disease sites. With a state of the art 4D optimization, intensity modulated particle therapy (IMPT) was able to generate treatment plans with less OAR dose and comparable target coverage to SBRT. It was possible to generate a single fraction plan with IMPT for a specific patient, where SBRT was limited due to a high heart dose.

Treatment of NSCLC with PT is influenced by interplay between tumor motion and beam scanning. It was shown that rescanning offers an adequate motion mitigation.

PT offers a precise dose shaping and it can be thus more prone to uncertainties. Calculation of time-resolved (4D) doses can be significantly affected by errors in deformable image registration - DIR [Heath and Seuntjens, 2006]. Special tools were developed in the scope of this thesis to ensure DIR quality assurance (DIRQA). Tools were tested on a large dataset to ensure their validity.

1.1 Deformable image registration and validation

A single DIR algorithm was used in this study, B-Spline. In contrast to Demons algorithm, B-Spline should handle large deformations, present in lung and cardiac 4D-CT, well [Tang et al., 2013]. The DIR for lung 4D-CT had only little inconsistencies and can be B-Spline can be considered sufficient. On the other hand, the results suggest that B-Spline is inadequate for DIR of a pig cardiac 4D-CT. The parameters used in B-Spline DIR were similar in both cases of DIR. This could be improved by investigating the effect of parameters on DIR quality.

The advantage of using open-source software for DIR, as explained in Section **??** is that different DIR algorithms, optimization metrics and image types can be used. They can be accessed either with using existing libraries, such as ITK [Yoo et al., 2002], or by writing designated software [Fedorov et al., 2015]. In future, different DIR algorithms have to be implemented and tested for various anatomical sites.

In this study, DIR was used in contour propagation, 4D optimization and 4D dose calculation. The 4D optimization and 4D dose calculation require accurate DIR in each voxel. This was ensured by calculating DIRQA voxel-wise.

Tests in DIRQA module were divided into two groups - qualitative and quantitative. Qualitative tests are false color and checkerboard and they provide a clear overview of the DIR result. However they do not give any infromation of vector field quality. An example of the disadvantage of the qualitative test could be seen in pig cardiac 4D-CT, where qualitative test did not show any errors in DIR, but errors were observed in vector fields.

The quantitative tests used in DIRQA module are landmark distance, absolute difference, Jacobian and ICE. Absolute difference, Jacobian and ICE have undergone an extensive testing. The results suggest that absolute difference gives us the least information about DIRQA, apart that it has to be lower after the DIR. We have shown that bigger deformations yield more deviations in Jacobian and ICE, which was also previously reported [Stanley et al., 2013]. Furthermore, we have confirmed that Jacobian should always be positive for a successful DIR [Rey et al., 2002]. Additionally, our results show that ICE should be smaller than maximum vector field magnitudes. Any deviations from mentioned trends should be thoroughly examined.

There are additional vector fields validation methods beside Jacobian and ICE, such as vector field curl [Schreibmann et al., 2012], unbalanced energy [Zhong et al., 2007], permutation and analysis of variance (ANOVA) tests [Klein et al., 2009]. It was demonstrated in a study by Salguero et al [Salguero et al., 2011] that DIR errors greater than 1 mm can lead to large dose errors in high-dose gradient regions. Therefore the DIR accuracy has to be quantified at each image voxel in the high-dose gradient regions. In our study a focus was given on a complete registration to find potential errors. However, in future studies the regions of interest used should be around the target, where high-dose gradients can occur. Furthermore the effect of image and vector field downsampling on DIRQA and on 4D dose calculation should be assessed.

Due to the lack of landmarks in all 4D-CTs landmark distance was not included in verification. Two contour based validation, dice similarity coefficient [Varadhan et al., 2013] and Hausdorff distance [Huttenlocher et al., 1993] are planned to be implemented in the DIRQA module. In literature many different attempts have been done to asses DIRQA with landmarks or contours. A study by Hardcastle et al [Hardcastle et al., 2012] compared demons and Salient-Feature-Based registration with dice coefficient between propagated and physician drawn contours. A multi-institutional study by Brock et al [Brock, 2010] compared differences in propagated and oncologist drawn landmarks. A method has been developed by Castillo et al [Castillo et al., 2009] to automatically identify landmark points in lung patients images. However, visual based evaluations are limited in regions of uniform image intensity and by the number of the objects being tracked [Kashani et al., 2008, Liu et al., 2012].

1.2 Treating non-small cell lung cancer with particle therapy

The results in this thesis suggest, that PT could be used as a treatment modality for NSCLC. It delivers comparable target dose to SBRT, while significantly reducing dose to OARs. The lower mean heart could be crucial in improving patient survival based on a recent trial from RTOG 0617 [Bradley et al., 2015]. The mean dose to heart would be on average 1 Gy smaller with PT than with SBRT. For patients with multiple disease sites it would be 4 Gy smaller. Similar results were observed when comparing protons to SBRT [Georg et al., 2008].

Compared to SBRT there is less overall dose deposited to the patient due to the narrow channel of PT, which can be seen on dose baths in Fig. **??** and **??**. Hence the benefit of PT is most profond for patients with large total target volume, wheter a large single target or multiple targets. Studies suggest, that SBRT is limited for large tumors (radius $>$ 5 cm) and multiple primary tumors [Timmerman et al., 2006, Georg et al., 2008, Westover et al., 2012], making PT a promising alternative.

Besides large tumors and multiple primary tumors, SBRT is also limited in treating centrally located tumors and tumors close to the chest wall. In a study done at Francis H. Burr Proton Therapy Center patients who could not be treated with SBRT, due to the scenarios mentioned, were treated with passive proton beam in 3 - 5 fractions, delivering 42 - 50 Gy [Westover et al., 2012]. They observed similar tumor local control rates as in SBRT (100% in a two year follow-up) with limited toxicities. It should be stressed that these patients were rejected from SBRT treatment due to the complexity and regardless proton therapy achieved similar results to SBRT.

Beside narrow entry channel, PT has sharper dose gradients and can conform the dose better to the target. Fig **??** shows that 80% of the targets have $D_{99\%}$ between 100 - 107% and 100 and 102% for SBRT and PT, respectively. Sharper dose gradients also enable less dose to the surrounding tissue. Nevertheless, fraction escalation was possible only in one patient out of three. The limitation in two patients with unsuccessful fraction escalation was esophagus maximum single point dose D_{Max}, which is 15 Gy in 1 x 24 Gy scheme. In both patients the esophagus was closer than 2 mm to the target, making the limitation impossible to respect without sacrificing the target dose. Furthermore, for one of these two patients, the PT could not deliever planned target dose, whereas SBRT could. Beside complex geometry, the tumor had a small volume and large motion. This patient exhibit the advantage of SBRT over PT.

PT has to take into account particle range uncertanity, which can come from the conversion of HU units to stopping power [Schneider et al., 1996] or from anatomical changes in the patient [Unkelbach et al., 2009]. We included range uncertainties with expansion of taret in beam's eye view, which resulted on average in 1.5 times bigger target volume for PT compared to SBRT. Another way to include range and other uncertainties is robust optimization, which makes IMPT plans more resiliant to uncertainties [Unkelbach et al., 2009, Chen et al., 2012]. We are

planning to include robust optimization in a future study, where SFUD, IMPT and robust IMPT plans will be compared for NSCLC patients.

While tumor motion influences photon treatment, it can be mittigated with proper margins [Zou et al., 2014]. On the other hand, effects can be substantial when treating moving targets with scanned particle therapy [Bert et al., 2008]. It was shown in this thesis that rescanning is an adequate motion mitigation technique. However, rescanning has a degree of uncertanity, especially regarding OAR D_{Max}. In hypofractionated treatment this limits are strict and exact dose to the OAR must be known. A possible solution would be to simulate rescanning and 4D delivery in optimization process itself. Such solution is not yet feasible due to the complexity of the problem. Another solution could also be phase-controled resanning [Mori et al., 2013, Takahashi et al., 2014]. However, it requires motion monitoring and complicates treatment delivery.

The gating is a comonnly used motion mitigation technique in a photon and particle treatment. While it provides less motion-induced dose errors, it prolongs treatment time. A recent study by Zhang et al [Zhang et al., 2015] included different breathing patterns, obtained from a MRI, on a 4D-CT and calculated 4D doses for liver cancer patients treated with proton therapy. They have shown that a gating window of 3 mm can result in a 10% efficiency of a duty-cycle, substantially prolonging treatment. Additionally, they have shown that neither volumetric or slice-by-slice rescanning could achieve good target coverage. However, good target coverage was obtained with combination of gating and rescanning. Their results suggest that a combination of gating and rescanning would currently be the best solution for treating NSCLC patients with PT.

Between rescanning, gating and beam tracking beam tracking is the most precise technique, since it requires no internal target margins [Bert and Durante, 2011]. Current clinical implementations of tracking in photon radiotherapy [Kilby et al., 2010, Keall et al., 2014] can not be directly used in particle therapy, since they only provide the position of single internal points. Fassi et al [Fassi et al., 2015] were able to account for inter- and intra-fractional variability of patient's anatomical configuration with a designated modeling technique [Fassi et al., 2014]. The measured median of water-equivalent path length in target was within 2 mm of a simulated one. For actual clinical impementation it will be necesarry to test the model on a large patient dataset.

All three techniques, rescanning, gating and beam tracking, essentially adapt 3D treatment plan to a 4D situation and thus have limitations. Full 4D-optimization, on the other hand, creates a 4D treatment plan, with each motion state in 4D-CT having designated treatment plan. A full 4D-optimization has been successfully implemented and verified experimentally at GSI [Graeff et al., 2013].

In a recent phase II study by Iyengar et al [Iyengar et al., 2014] patiens with stage IV NSCLC were treated with SBRT and chemotherapy. They have irradiated 52 targets in 24 patients, 16

of them had more than one target. The results were promising, with 20 months median overall survival, compared to 9 months when treating with chemotherapy only [Tsao, 2016]. Results in this thesis show, that patients with multiple disease sites would especially benefit from PT. Based on the poor prognosis of stage IV NSCLC patients and on the results published by Iyengar et al, stage IV NSCLC patients could be eligible candidates for PT treatment. Additionally, such patients usually exhibit chronic obstructive pulmonary disease and less dose to the lung is warranted [Westover et al., 2012]. This further supports our claim, since our study showed substantial differences in doses to ipsilateral lung ($V_{20\%}$ was on average 15% smaller in PT for patients with multiple disease sites) and contralateral lung as well - 70% of patients did not receive any dose to the contralateral lung, whereas SBRT deposited dose in contralateral lung in all patients.

The results of a multi-institutional randomized trial, RTOG1308 [RTOG, 2014], comparing photons and particle therapy in treating NSCLC, will have an important impact on treating NSCLC. The trial started in 2014.

1.2.1 Outlook

Recent advances in photon radiotherapy allow the usage of noncoplanar beams, a so-called 4π optimization [Dong et al., 2013b]. A study by Dong et al [Dong et al., 2013a] showed that 4π yielded better target coverage and OAR sparing than SBRT for NSCLC patients. They have reported reduction of D_{Max} in heart, esophagus and spinal cord by 32%, 72% and 53%, respectively, showing the potential of a 4π optimization. According to this thesis, PT is able to reduce the D_{Max} even further, with a reduction of 57%, 87% and 83% for heart, esophagus and spinal cord, respectively. The numbers, however, should be compared with caution, since they were obtained from a different set of patients. A future study, directly comparing SBRT, 4π and PT for NSCLC is thus warranted.

Robust optimization seems to be gaining on popularity for PT. Standard margin defenition to account for uncertainties fails short in PT, while the inclusion of uncertainties in optimization process can substantially improve treatment plans [Chen et al., 2012]. The robstuness optimization is now possible even for a 4D optimization [Liu et al., 2016], opening a wide field of new possibilities.

Bibliography

[Bert and Durante, 2011] Bert, C. and Durante, M. (2011). Motion in radiotherapy: particle therapy. *Physics in Medicine and Biology*, 56(16):R113–R144.

[Bert et al., 2008] Bert, C., Groezinger, S. O., and Rietzel, E. (2008). Quantification of interplay effects of scanned particle beams and moving targets. *Phys. Med. Biol.*, 53(9):2253–2265.

[Bradley et al., 2015] Bradley, J. D., Paulus, R., Komaki, R., Masters, G., Blumenschein, G., Schild, S., Bogart, J., Hu, C., Forster, K., Magliocco, A., Kavadi, V., Garces, Y. I., Narayan, S., Iyengar, P., Robinson, C., Wynn, R. B., Koprowski, C., Meng, J., Beitler, J., Gaur, R., Curran, W. J., and Choy, H. (2015). Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage iiia or iiib non-small-cell lung cancer (rtog 0617): a randomised, two-by-two factorial phase 3 study. *The Lancet Oncology*, 16(2):187–199.

[Brock, 2010] Brock, K. K. (2010). Results of a multi-institution deformable registration accuracy study (midras). *Int. J. Radiat. Oncol. Biol. Phys.*, 76(2):583–596.

[Castillo et al., 2009] Castillo, R., Castillo, E., Guerra, R., Johnson, V. E., McPhail, T., Garg, A. K., and Guerrero, T. (2009). A framework for evaluation of deformable image registration spatial accuracy using large landmark point sets. *Physics in Medicine and Biology*, 54(7):1849.

[Chen et al., 2012] Chen, W., Unkelbach, J., Trofimov, A., Madden, T., Kooy, H., Bortfeld, T., and Craft, D. (2012). Including robustness in multi-criteria optimization for intensity-modulated proton therapy. *Physics in Medicine and Biology*, 57(3):591–608.

[Dong et al., 2013a] Dong, P., Lee, P., Ruan, D., Long, T., Romeijn, E., Low, D. A., Kupelian, P., Abraham, J., Yang, Y., and Sheng, K. (2013a). 4pi noncoplanar stereotactic body radiation therapy for centrally located or larger lung tumors. *International Journal of Radiation Oncology*Biology*Physics*, 86(3):407 – 413.

[Dong et al., 2013b] Dong, P., Lee, P., Ruan, D., Long, T., Romeijn, E., Yang, Y., Low, D., Kupelian, P., and Sheng, K. (2013b). 4pi non-coplanar liver sbrt: A novel delivery technique. *International Journal of Radiation Oncology*Biology*Physics*, 85(5):1360 – 1366.

[Fassi et al., 2014] Fassi, A., Schaerer, J., Fernandes, M., Riboldi, M., Sarrut, D., and Baroni, G. (2014). Tumor tracking method based on a deformable 4d {CT} breathing motion

model driven by an external surface surrogate. *International Journal of Radiation Oncology*Biology*Physics*, 88(1):182 – 188.

[Fassi et al., 2015] Fassi, A., Seregni, M., Riboldi, M., Cerveri, P., Sarrut, D., Ivaldi, G. B., de Fatis, P. T., Liotta, M., and Baroni, G. (2015). Surrogate-driven deformable motion model for organ motion tracking in particle radiation therapy. *Physics in Medicine and Biology*, 60(4):1565.

[Fedorov et al., 2015] Fedorov, A., Khallaghi, S., Sánchez, C., Lasso, A., Fels, S., Tuncali, K., Sugar, E. N., Kapur, T., Zhang, C., Wells, W., Nguyen, P., Abolmaesumi, P., and Tempany, C. (2015). Open-source image registration for mri-trus fusion-guided prostate interventions. *Int J Comput Assist Radiol Surg*, 10(6):925–34.

[Georg et al., 2008] Georg, D., Hillbrand, M., Stock, M., Dieckmann, K., and Pötter, R. (2008). Can protons improve sbrt for lung lesions?: Dosimetric considerations. *Radiotherapy and Oncology*, 88(3):368–375.

[Graeff et al., 2013] Graeff, C., Lüchtenborg, R., Eley, J. G., Durante, M., and Bert, C. (2013). A 4d-optimization concept for scanned ion beam therapy. *Radiotherapy and Oncology*, 109(3):419 – 424.

[Hardcastle et al., 2012] Hardcastle, N., Tomé, W. A., Cannon, D. M., Brouwer, C. L., Wittendorp, P. W., Dogan, N., Guckenberger, M., Allaire, S., Mallya, Y., Kumar, P., Oechsner, M., Richter, A., Song, S., Myers, M., Polat, B., and Bzdusek, K. (2012). A multi-institution evaluation of deformable image registration algorithms for automatic organ delineation in adaptive head and neck radiotherapy. *Radiat Oncol*, 7:90–90.

[Heath and Seuntjens, 2006] Heath, E. and Seuntjens, J. (2006). A direct voxel tracking method for four-dimensional monte carlo dose calculations in deforming anatomy. *Medical Physics*, 33(2).

[Huttenlocher et al., 1993] Huttenlocher, D. P., Klanderman, G. A., and Rucklidge, W. J. (1993). Comparing images using the hausdorff distance. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 15(9):850–863.

[Iyengar et al., 2014] Iyengar, P., Kavanagh, B. D., Wardak, Z., Smith, I., Ahn, C., Gerber, D. E., Dowell, J., Hughes, R., Camidge, D. R., Gaspar, L. E., Doebele, R. C., Bunn, P. A., Choy, H., and Timmerman, R. (2014). Phase ii trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J.Clin.Oncol.*, 32(34):3824–3854.

[Kashani et al., 2008] Kashani, R., Hub, M., Balter, J. M., Kessler, M. L., Dong, L., Zhang, L., Xing, L., Xie, Y., Hawkes, D., Schnabel, J. A., McClelland, J., Joshi, S., Chen, Q., and Lu,

W. (2008). Objective assessment of deformable image registration in radiotherapy: A multi-institution study. *Medical Physics*, 35(12):5944–5953.

[Keall et al., 2014] Keall, P. J., Colvill, E., O?Brien, R., Ng, J. A., Poulsen, P. R., Eade, T., Kneebone, A., and Booth, J. T. (2014). The first clinical implementation of electromagnetic transponder-guided mlc tracking. *Medical Physics*, 41(2).

[Kilby et al., 2010] Kilby, W., Dooley, J. R., Kuduvalli, G., Sayeh, S., and C. R. Maurer, J. (2010). The cyberknife robotic radiosurgery system in 2010. *Technol. Cancer Res. Treat.*, 9(5):433–452.

[Klein et al., 2009] Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M.-C., Christensen, G. E., Collins, D. L., Gee, J., Hellier, P., Song, J. H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R. P., Mann, J. J., and Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain mri registration. *Neuroimage*, 46(3):786–802.

[Liu et al., 2012] Liu, F., Hu, Y., Zhang, Q., Kincaid, R., Goodman, K. A., and Mageras, G. S. (2012). Evaluation of deformable image registration and motion model in ct images with limited features. *Phys Med Biol*, 57(9):2539–2554. 22491010[pmid].

[Liu et al., 2016] Liu, W., Schild, S. E., Chang, J. Y., Liao, Z., Chang, Y.-H., Wen, Z., Shen, J., Stoker, J. B., Ding, X., Hu, Y., Sahoo, N., Herman, M. G., Vargas, C., Keole, S., Wong, W., and Bues, M. (2016). Exploratory study of 4d versus 3d robust optimization in intensity modulated proton therapy for lung cancer. *International Journal of Radiation Oncology*, 95(1):523–533.

[Mori et al., 2013] Mori, S., Furukawa, T., Inaniwa, T., Zenklusen, S., Nakao, M., Shirai, T., and Noda, K. (2013). Systematic evaluation of four-dimensional hybrid depth scanning for carbon-ion lung therapy. *Med Phys.*, 40(3):031720.

[Rey et al., 2002] Rey, D., Subsol, G., Delingette, H., and Ayache, N. (2002). Automatic detection and segmentation of evolving processes in 3d medical images: application to multiple sclerosis. *Med Image Anal*, 6(2):163–179.

[RTOG, 2014] RTOG (2014). Rtog 1308 protocol information: Phase iii randomized trial comparing overall survival after photon versus proton chemoradiotherapy for inoperable stage ii-iiib nsclc.

[Salguero et al., 2011] Salguero, F. J., Saleh-Sayah, N. K., Yan, C., and Siebers, J. V. (2011). Estimation of three-dimensional intrinsic dosimetric uncertainties resulting from using deformable image registration for dose mapping. *Medical Physics*, 38(1):343–353.

[Schneider et al., 1996] Schneider, U., Pedroni, E., and Lomax, A. (1996). The calibration of ct hounsfield units for radiotherapy treatment planning. *Physics in Medicine and Biology*, 41(1):111.

[Schreibmann et al., 2012] Schreibmann, E., Pantalone, P., Waller, A., and Fox, T. (2012). A measure to evaluate deformable registration fields in clinical settings. *Journal of Applied Clinical Medical Physics*, 13(5).

[Stanley et al., 2013] Stanley, N., Glide-Hurst, C., Kim, J., Adams, J., Li, S., Wen, N., Chetty, I. J., and Zhong, H. (2013). Using patient-specific phantoms to evaluate deformable image registration algorithms for adaptive radiation therapy. *J Appl Clin Med Phys*, 14(6):4363–4363.

[Takahashi et al., 2014] Takahashi, W., Mori, S., Nakajima, M., Yamamoto, N., Inaniwa, T., Furukawa, T., Shirai, T., Noda, K., Nakagawa, K., and Kamada, T. (2014). Carbon-ion scanning lung treatment planning with respiratory-gated phase-controlled rescanning: simulation study using 4-dimensional ct data. *Radiation Oncology*, 9:238.

[Tang et al., 2013] Tang, C., Xie, X., and Du, R. (2013). Improved image registration technique using demons and b-spline. *Biomedical and Biotechnology Engineering*, 3(A).

[Timmerman et al., 2006] Timmerman, R., McGarry, R., Yiannoutsos, C., Papiez, L., Tudor, K., DeLuca, J., Ewing, M., Abdulrahman, R., DesRosiers, C., Williams, M., and Fletcher, J. (2006). Excessive toxicity when treating central tumors in a phase ii study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *Journal of Clinical Oncology*, 24(30):4833–4839.

[Tsao, 2016] Tsao, A. S. (2016). Lung carcinoma. Merck Manual Professional Edition.

[Unkelbach et al., 2009] Unkelbach, J., Bortfeld, T., Martin, B. C., and Soukup, M. (2009). Reducing the sensitivity of impt treatment plans to setup errors and range uncertainties via probabilistic treatment planning. *Med Phys*, 36(1):149–163. 074812MPH[PII].

[Varadhan et al., 2013] Varadhan, R., Karangelis, G., K., K., and Hui, S. (2013). A framework for deformable image registration validation in radiotherapy clinical applications. *J Appl Clin Med Phys*, 14(1).

[Westover et al., 2012] Westover, K. D., Seco, J., Adams, J. A., Lanuti, M., Choi, N. C., Engelsman, M., and Willers, H. (2012). Proton sbrt for medically inoperable stage i nsclc. *J Thorac Oncol*, 7(6):1021–1025. 22551902[pmid].

[Yoo et al., 2002] Yoo, T. S., Ackerman, M. J., Lorensen, W. E., Schroeder, W., Chalana, V., Aylward, S., Metaxas, D., and Whitaker, R. (2002). Engineering and algorithm design for an

image processing api: a technical report on itk–the insight toolkit. *Stud Health Technol Inform*, 85:586–592.

[Zhang et al., 2015] Zhang, Y., Knopf, A.-C., Weber, D. C., and Lomax, A. J. (2015). Improving 4d plan quality for pbs-based liver tumour treatments by combining online image guided beam gating with rescanning. *Physics in Medicine and Biology*, 60(20):8141.

[Zhong et al., 2007] Zhong, H., Peters, T., and Siebers, J. V. (2007). Fem-based evaluation of deformable image registration for radiation therapy. *Physics in Medicine and Biology*, 52(16):4721.

[Zou et al., 2014] Zou, W., Yin, L., Shen, J., Corradeti, M. N., Kirk, M., Munbodh, R., Fang, P., Jabbour, S. K., Simone, C. B., Yue, N. J., Rengan, R., and Teo, B. K. (2014). Dynamic simulation of motion effects in imat lung sbrt. *Radiation Oncology*, 9:225.