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 plan for a a single fraction ablative dose with IMPT for a specific patient, where SBRT was limited due to excessive heart dose.

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

PT offers precise dose shaping but it can thus also be 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 well as present in lung and cardiac 4D-CT [Tang et al., 2013]. The DIR for lung 4D-CT had only small inconsistencies and here 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 systematically 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 using existing libraries, such as ITK [Yoo et al., 2002], or by writing designated software [Fedorov et al., 2015]. In the future, different DIR algorithms have to be implemented and tested for various anatomical sites.

In this study, DIR was used in contour propagation and 4D dose calculation. The 4D dose calculation requires accurate DIR in each voxel, since dose is propagated with vector field. This was ensured by calculating vector field Jacobian and ICE voxel-wise.

Tests in DIRQA module were divided into two groups - qualitative and quantitative. Qualitative tests are false color and checkerboard; they provide an overview of the DIR result. However they do not give any information of vector field quality and it is impossible to review the sheer amount of data. 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 the 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 the verification. Two contour based validations, dice similarity coefficient [Varadhan et al., 2013] and Hausdorff distance [Huttenlocher et al., 1993] are planned to be implemented in the DIRQA module. In the literature many approaches have been reported to assess DIRQA with landmarks or contours. A study by Hardcastle et al. [Hardcastle et al., 2012] compared demons and Salient-Feature-Based registration with dice coefficients 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 of limited use in regions of uniform image intensity and by the number of the objects being tracked [Kashani et al., 2008, Liu et al., 2012].

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 on average 4 Gy smaller, reaching up to 9 Gy. Similar results were observed when comparing protons to SBRT [Georg et al., 2008].

The advantageous dose profile of PT permits to use few, selected fields with narrow entry channels, avoiding the dose bath needed in SBRT to achieve high dose gradients in the target. Hence the benefit of PT is most profound for patients with large total target volume, whether 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.

In addition to the 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 the two patients with unsuccessful fraction escalation was the 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 target dose. Furthermore, for one of these two patients, PT could not deliver planned target dose, whereas SBRT could. Beside complex geometry, the tumor had a small volume and large motion. This patient exhibits the advantage of SBRT over PT.

PT has to take into account particle range uncertainty, which can come from the conversion of HU 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 target 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, resulting in IMPT plans more resilient 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 mitigated 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 uncertainty, especially regarding OAR D_{Max}. In hypofractionated treatment these limits are strict and exact dose to the OAR must be known. A possible solution would be to simulate rescanning and 4D delivery in the optimization process itself. Such a solution is not yet feasible due to the complexity of the problem. Another solution could also be phase-controlled rescanning with greatly reduced uncertainty in the mitigation outcome [Mori et al., 2013, Takahashi et al., 2014]. However, it requires motion monitoring and complicates treatment delivery.

Gating is a commonly used motion mitigation technique in both 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 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, this 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 implementation it will be necessary 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 the 4D-CT having a 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] patients 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 use of non-coplanar 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 definition to account for uncertainties fails in PT, while the inclusion of uncertainties in optimization process can substantially improve treatment plans [Chen et al., 2012]. The robustness optimization is now computationally possible even for a 4D optimization [Liu et al., 2016], opening a wide field of new possibilities.

2 Conclusion

Scanned carbon-ions (PT) should be considered as a treatment modality for non-small cell lung cancer. Beside delivering the same dose to tumors as the state of the art photon therapy (SBRT), PT tremendously reduces normal tissue irradiation.

PT would be especially beneficial for patients with large tumors or with multiple disease sites, because the dose bath is much smaller than with SBRT. This could be exploited even further and for some patients PT could deliver dose in a single fraction, whereas SBRT could not due to over irradiating normal tissue.

To ensure tumor will receive the planned dose and the dose to the normal tissue will not exceed prescribed limits, it is imperative to include a time-resolved (4D) dose calculation in a PT treatment planning. A 4D dose calculation is based on the deformable image registration (DIR). A DIR is a complex problem and hence prone to errors. Since any errors in DIR may significantly affect the 4D dose calculation, a DIR quality assurance must be conducted before using DIR in the PT treatment planning for lung cancer.

Patients with advanced staged lung cancer have an extremely poor prognosis, with a median survival of only nine months. Currently the best treatment is a combination of chemotherapy and SBRT. However, more than 10% of the patients will die due to treatment-related effects. Based on the results shown in this thesis, PT could significantly reduce the treatment-related side effects and hence tremendously improve the survival for lung cancer patients.

Bibliography