1 Discussion

This is a first in silico study directly comparing clinical stereotactic body radiation therapy (SBRT) with scanned carbon-ions (PT) treatment plans for non-small cell lung cancer (NSCLC). Our results show, that carbon-ions could be considered an alternative to SBRT, with the same tumor coverage and less dose to OAR.

Since PT offers a precise dose shaping, it can be more prone to uncertainties and a special consideration must be paid to them. Calculation of time-resolved (4D) doses can be significantly affected by errors in deformable image registration (DIR) **Citat**. Special tools were developed in the scope of this thesis to ensure DIR quality assurance (DIRQA). Additionally, DIRQA was tested on a large dataset for a tool verification. Treatment of NSCLC with PT is also influenced by interplay between tumor motion and beam scanning. It was shown that rescanning offers an adequate motion mitigation. Additionally, a prospect for treating patients with multiple lung metastases was displayed.

1.1 Deformable image registration

With features such as adaptive treatment planning [Yan et al., 1997], 4D optimization [Trofimov et al., 2005], 4D dose calculation [Flampouri et al., 2006], contour propagation [Lu et al., 2006] and combining different imaging modalities [Leibfarth et al., 2013] DIR is slowly entering everyday clinical work-flow. There are various different registration algorithms available [Varadhan et al., 2013] along with different optimization metrics, such as mean square error, cross-correlation, or normalized mutual information [Glocker et al., 2011].

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. Either with using existing libraries, such as ITK [Yoo et al., 2002], or by writing designated software [Fedorov et al., 2015]. A B-Spline algorithm was used for DIR in this thesis. There are large deformations present in lung and cardiac 4D-CT, which B-Spline should handle well [Tang et al., 2013]. The mean square error metric also gives better results for images of the same modality and same contrast [Varadhan et al., 2013]. The comparison between different algorithms and optimization metrics is beyond the scope of this thesis.

1.1.1 Deformable image registration validation

Any DIR algorithm must undergo thorough evaluation before it can be used clinically. The most common practice for DIRQA is visual validation [Stanley et al., 2013]. Our DIRQA module offers false color, checkerboard and landmarks distance as visual validation methods. Contour validation is currently lacking in our 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]. An example of visual validation disadvantage could be seen in pig cardiac 4D-CT, where visual evaluation did not show any errors in DIR, but errors were observed in vector fields resulting from DIR.

An alternative to visual validation is to evaluate mathematical properties of vector fields. The two most common DIR vector fields evaluation metrics are Jacobian determinant (Jacobian) and inverse consistency error (ICE) [Leow et al., 2007, Christensen and Johnson, 2001], which we also implemented. We have shown that bigger deformations yield more deviations in Jacobian and ICE, which was also found by Stanley et al [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 deviation from this checks 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 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. A solution to evaluate at each specific voxel and for patient-specific registration was given by Stanley at al [Stanley et al., 2013]. They proposed a computational phantoms and their deformations with a finite element module framework.

Surgery is the gold standard in treating NSCLC in the early stages [Roesch et al., 2014]. In recent years, however, SBRT showed similar results as surgery and SBRT is recommended for all high-risk surgical patients. In a recent comparison study by Yu et al [Yu et al., 2015], SBRT had lower intermediate mortality and toxicity, compared to surgery. However, patients with long life expectancies were found to benefit more from surgery.

There are several clinical scenarios where use of SBRT might be limited. This include treatment of centrally located tumors, tumors close to chest wall, large tumors (radius > 5 cm) and multiple primary tumors [Timmerman et al., 2006, Georg et al., 2008, Westover et al., 2012]. The limitation of SBRT could open possibilities to other treatment modalities, such as particle therapy. Interestingly, two of the mentioned scenarios, large tumors and multiple tumors, would benefit the most from particle therapy, according to the results shown in this thesis and to the results published by Kadoya et al [Kadoya et al., 2010]. 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 noted, that the patients treated were rejected from SBRT treatment.

While treatment for early stage NSCLC is well established, more than 75% NSCLC cases present themselves in an advance stage [Jemal et al., 2009], usually due to the lack of detection in the early stages. The standard of care for advanced NSCLC is concurrent chemotherapy [Oshiro et al., 2014]. Dose escalation studies showed favorable prognosis for doses higher than 70 Gy [Hayman et al., 2001, Rosenman et al., 2002, Socinski et al., 2008]. The results of recent phase 3 randomized trial by Bradley et al [Bradley et al., 2010], however, showed better survival rates for patients delivered 60 Gy, instead of 74 Gy. It was speculated that higher doses to heart and esophagus might have contributed to higher mortality rates for patients who were administered higher doses [Cox, 2012]. Results presented in this thesis show that mean dose to heart and esophagus would be on average 1 Gy smaller with PT than with SBRT. Similar results were observed when comparing protons to SBRT [Georg et al., 2008].

Manjka se multiple 4pi Motion current status future?

RBE

24Gy(RBE)

Hypo-fractionation of liver cancer

Future SBRT - 4pi SBRT in lung cancer will become standard

Overview of lung cancer

Reoccurent lung cancer

Heart and esophagus dose good predictors of mortality RTOG 0917 median survival 19.5 months vs 29.4 months with protons (http://www.ncbi.nlm.nih.gov/pubmed/24864278) for 74 Gy, but was 29 for 60 Gy with photons as well.

Photons vs Protons for stage III NSCLC RTOG 1308

Stephen Bowen - deliever more dose to damaged lung instead of functionated one

bio-adaptive particle therapy

SBRT is the lowest for cost per quality of life for early stage, but Protons beams scanning for advanced SBRT limited: large tumors (>5 cm, more tumors, patients with poor lung funtction)

Proton SBRT

Seattle treated NSCLC with PBS

ABS vs passive?

Small tumor are bad

dosimetric study of protons vs sbrt

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