

In Silico Comparison of Photons versus Carbon Ions in Single Fraction Therapy of Lung Cancer

Title auf Deutsch

Zur Erlangung des Grades eines Doktors der Naturwissenschaften (Dr. rer. nat.)

vorgelegte Dissertation von Kristjan Anderle aus Jesenice, Slowenien

Tag der Einreichung:

1. Gutachten: Prof. Dr. Marco Durante

2. Gutachten: Prof. Dr. Thomas Aumann



TECHNISCHE
UNIVERSITÄT
DARMSTADT



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Abstract

Stereotactic body image guided radiation therapy (SBRT) shows good results for lung cancer treatment. However, complications can arise at the end or during the treatment. Better normal tissue sparing might be achieved with scanned carbon ion therapy (PT) and hence reduce the number of complications. Therefore an in silico trial was conducted to find potential advantages of PT in treating lung cancer. A study included patients that were treated with SBRT at Champalimaud Center for the Unknown, Lisbon (Portugal). PT plans were calculated on 4D-CTs with different breathing motion patterns simulated. A special investigation was made into patients with multiple lung disease sites, where two 4D optimization techniques were used. For successful simulations deformable image registration was used and a tool to provide its quality assurance has been developed.

The results showed that target coverage was comparable in SBRT and PT, while PT delivered less dose to critical structures, including heart, spinal cord, esophagus, trachea and aorta. Additionally, motion was successfully mitigated with resanning.

Zusammenfassung



Publications related to this work

GSI scientific reports

Anderle K., Stroom J., Pimentel J., Greco C., Durante M. and Graeff C.: An in silico Trial of X-rays vs Carbon Ions in Single Shot Lung Cancer Therapy; *GSI Scientific Report 2013*, 228

Conference contributions

Anderle K., Stroom J., Pimentel J., Greco C., Durante M. and Graeff C. (2013). An in silico Comparison of Scanned Carbon Ion vs. SBRT Single Dose Treatment of Metastatic Lung Cancer; *4D Treatment planning workshop*. Poster presentation

Anderle K., Stroom J., Pimentel J., Greco C., Durante M. and Graeff C. (2014). An in silico Comparison of Single Fraction Scanned Carbon Ion vs. SBRT in Metastatic Lung Cancer; *ESTRO*. Poster presentation

Anderle K., Stroom J., Pimentel J., Greco C., Durante M. and Graeff C. (2015). In Silico Trial of Photons versus Carbon Ions in Single Fraction Therapy of Lung Cancer; *PTCOG*. Poster presentation

Anderle K., Stroom J., Pimentel J., Greco C., Durante M. and Graeff C. (2015). In Silico Trial of Photons versus Carbon Ions in Single Fraction Therapy of Lung Cancer; *DGMP*. Poster presentation

Prall M., Hild S., **Anderle K.** and Graeff C. (2016). Treatment Planning with an Adaptive Dose Grid; *PTCOG*. Poster presentation

Eichhorn A., Hild S., **Anderle K.** and Graeff C. (2016). Speed-up of plan delivery for intensity modulated particle therapy by splitting iso-energy slices according to beam intensity levels; *PTCOG*. Poster presentation

Vieira S., Stroom J., **Anderle K.**, Salas B., Pimentel N. and Greco C. (2016). Validation of freeware-based midventilation CT calculation for upper abdominal cancer patients; *ESTRO*. Poster presentation



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List of Abbreviations

3DCRT	three dimensional conformal radiotherapy	LET	linear energy transfer
4D-CT	time resolved computed tomography	LR	left-right
4Dopt	time resolved optimization	MLC	multileaf collimators
AP	anterior-posterior	MRI	magnetic resonance imaging
CiT	scanned carbon-ion therapy	NIRS	National Institute of Radiological Sciences
CT	computed tomography	noPM	no pacemaker
CTV	clinical target volume	OAR	organ at risk
$D_{99\%}$	minimum dose delivered to 99% of volume	PET	positron emission tomography
D_{Max}	maximum dose delivered to a single voxel	PM	pacemaker
D_{Mean}	mean dose delivered to volume	PMMA	polymethyl methacrylate
DIR	deformable image registration	PSI	Paul Scherer Institut
DIRQA	deformable image registration quality assurance	PTV	planning target volume
DNA	deoxyribonucleic acid	RBE	relative biological effectiveness
DSB	double strand breaks	RTOG	Radiotherapy Oncology Group
DVH	dose volume histogram	SA	smaller airways
FWHM	full width at half maximum	SI	superior-inferior
GSI	GSI Helmholtzzentrum für Schwerionenforschung GmbH	SBRT	stereotactic body radiotherapy
GTV	gross tumor volume	SDRT	single dose radiotherapy
HIT	Heidelberg Ion-Beam Therapy Centre	SFUD	single field uniform dose
HU	Hounsfield unit	SOBP	spread out Bragg peak
ECG	electrocardiography	SSB	single strand break
IES	iso-energy slice	TRIP	treatment planning for carbon ion radiotherapy
IMPT	intensity modulated particle therapy	$V_{20\%}$	volume which received at least 20% of the target dose (dose coverage)
IMRT	intensity modulated radiotherapy	VMAT	volumetric modulated arc therapy
indITV	field-independent internal target volume		
ITV	internal target volume		
LEM	local effect model		

Motivation

In 2013 every fourth death in Germany was due to cancer and approximately 45 000 deaths were from lung and bronchial cancer [German Federal Statistical Office, 2015]. In the last 30 years, there was a 180% increase of deaths due to lung and bronchial cancer for women [German Federal Statistical Office, 2015]. The standard course of treatment for lung cancer is surgery, chemotherapy, radiotherapy or a combination of these. Surgery is usually the first choice of treatment for early stages of lung cancer. In recent years, however, state of the art photon radiotherapy, called stereotactic body-radiation therapy (SBRT) showed promising results for treating lung cancer [Baumann et al., 2009, Greco et al., 2011]. SBRT delivers high doses (up to 24 Gy) in 1 - 5 fractions, therefore dose to critical structure must be carefully considered.

In the last twenty years, ion beam therapy has proven to be a promising alternative to photon radiotherapy. Higher tumor control rates and better dose conformity can be achieved with superior physical and biological ion properties, when compared to photons [Tsujii et al., 2008, Durante and Loeffler, 2010]. A recent review made by Kamada et al reported a high 3-year survival rate for carbon-ions (76.9%) for treating lung cancer in single fraction, with no late treatment-related complications [Kamada et al., 2016]. The treatment used passive beam scanning, where patient specific absorbers are used to conform the dose to the tumor. Active beam scanning, on the other hand, can provide even better dose shaping, which is essential in hypo-fractionated treatment. However, interaction between tumor and scanned beam motion, called interplay, can severely degrade dose distribution in patient. Therefore designated motion mitigation techniques must be used for successful treatment of lung cancer with active beam scanning [Bert et al., 2008].

Successful treatment of tumors in abdomen region (liver and pancreases tumors) with scanned ion beams has been already done at HIT, Heidelberg (Germany) and CNAO, Pavia (Italy) [Habermehl et al., 2013, Rossi, 2016] and first lung cancer patients are being treated at NIRS, Chiba (Japan) [Mori et al., 2016]. Studies on impact of scanned ion beam on lung cancer treatment are thus warranted, so eligible patients can be identified.

In this thesis we will address this challenges of treating lung cancer patients with active beam scanning and make a comparison between SBRT and scanned carbon-ion therapy. Patients particularly suited for carbon-ion therapy will try to be identified for a possible future treatment at designated facilities in Marburg and Heidelberg.

Scope of this work

This is the first *in silico* comparision between SBRT and active scanning carbon-ion for non-small cell lung cancer (NSCLC). A time-resolved (4D) doses will be studied on a large patient dataset, including patients with multiple metastases.

In order to create carbon-ion treatment plans and calculate 4D doses, contours have to be propagated from planning computed tomography (CT) to all motion states in 4D-CT. Additionally, motion between 4D-CT states has to be quantified. This will be achieved with deformable image registration (DIR). Furthermore, a designated tool for DIR quality assurance (DIRQA) will be developed. A verification of DIR and DIRQA has been done on a human lung 4D-CT and on pig cardiac 4D-CT dataset.

To show potential of scanned carbon-ions in handling NSCLC, treatment plans for 19 patients, which were actually treated with SBRT, will be calculated. Afterwards, static and 4D doses with and without motion mitigation will be analyzed. Doses to targets and organs-at-risk (OAR) will be analyzed and compared between carbon-ions and SBRT.

A special investigation will be made into patients with multiple NSCLC metastases. A treatment planning software will be modified, in order to handle multiple targets in a single patient. Treatment plans for patients with multiple NSCLC metastases will be generated with two different optimization techniques to tackle range changes in moving targets. Comparison to SBRT will be made regarding target coverage and OAR doses.

The structure of this dissertation is as follows. Chapter 1 will present an overview of physical and biological fundamentals of radiotherapy. Photon and particle radiotherapy will be presented, with an emphasis on the treatment of moving targets. Additionally, a description of lung cancer will be given. Chapter 2 will present tools to handle DIR and DIRQA and verification of these tools. In chapter 3, comparison between SBRT and carbon-ions will be investigated on lung cancer patients. Treatment for patients with multiple metastases in lung will be investigated in chapter 4. Overall results will be discussed in chapter 5 and the thesis will be concluded in chapter 6.



1 Introduction - research background and fundamentals

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1.1 Radiotherapy

An ionizing radiation was used for treating tumors since the discovery of X-rays in 1895. In the beginning only superficial diseases would be treated, but as time and technology progressed X-ray tubes gained on voltage, allowing treatment of deeper seated tumors.

The radiation from linear accelerator was first used in medicine in 1953. Because the beam is more collimated and energies are higher compared to X-ray tubes, the cure rates improved tremendously. The next big milestone was introduction of computers in the field of radiotherapy. This led to better diagnostic tools, such as computed tomography scans (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). With these tools the location of the tumor could be better estimated and hence the physicians could prescribe better treatment. The potential of computers was afterwards exploited also in the treatment planning process, resulting in intensity modulated radiation therapy (IMRT) which, together with diagnostic tools, provides an exact dose shaping in accordance to patient specific tumors.

In 1946, a paper from R. Wilson first described the application of protons for cancer treatment [Wilson, 1946]. It was shown that protons have preferable depth dose profile compared

to photons. First patient treatment soon followed in the early 1950's at Lawrence Berkeley Laboratory, USA. Heavier ions, such as ^2He , ^{20}Ne and ^{6}C were later also used for treatment. In the beginning only passive beam delivery (see Section 1.2.3) was used for treatment and in the 1990's active beam solutions (see Section 1.2.3) were developed at Paul Scherrer Institute (PSI), Villigen (Switzerland) for protons and at GSI, Darmstadt (Germany) for carbon ions.

1.2 Physical and biological basics of radiotherapy

The aim of radiotherapy is to kill tumor cells and prevent further growth, while sparing healthy tissue. Both radiotherapy modalities (photons and ions) use the same principle to eliminate cancer cells - they aim to damage the cell genetic material through ionization. The actual physical and biological mechanism behind both modalities will be explained in detail in the following section.

1.2.1 Interaction of radiation with matter

The interactions between photons with matter and ions with matter are quite different, as can be seen from depth dose distributions in Fig. 1.1. Photons deposit the highest local dose shortly after entering the matter (at the energies used in radiotherapy). Ions, on the other hand, deposit most of their dose right before they stop in the so-called Bragg Peak region. The position of the Bragg Peak depends on the energy of the ions, which is exploited in the treatment of deep seated tumors.

Dose definition

An important quantity in radiotherapy is dose, D , defined as the ratio of the absorbed energy dE per mass element dm [ICRU, 1993b]:

$$D = \frac{dE}{dm} \quad \left[\text{Gy} = \frac{\text{J}}{\text{kg}} \right] \quad (1.1)$$

Usually we can describe energy loss of a beam in a thin layer of material, dE/dx . Dose can be then rewritten as:

$$D = \frac{dE}{dx} \times \frac{1}{F} \times \frac{1}{\rho} \quad (1.2)$$

where F is the fluence and ρ the material density.

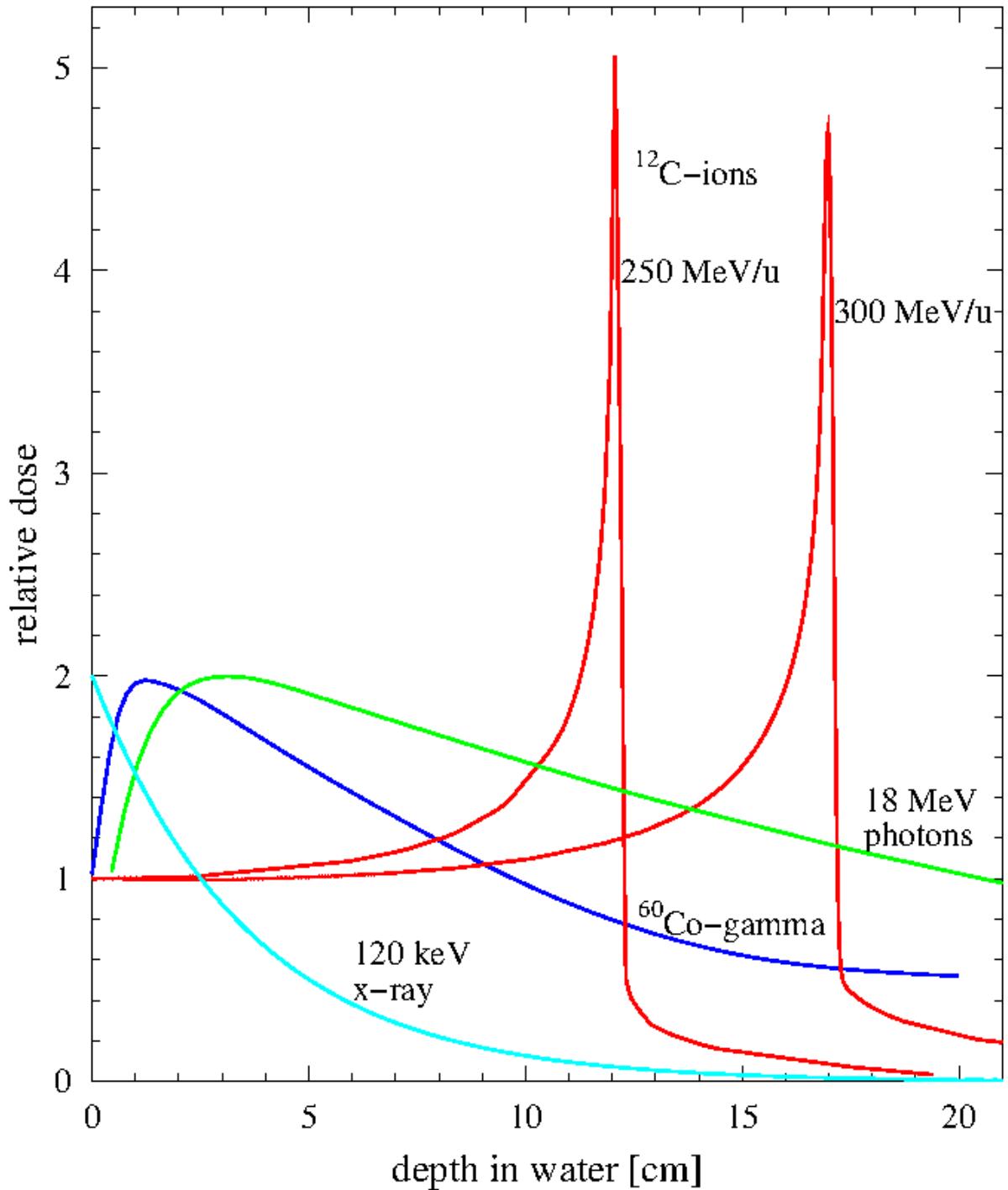


Figure 1.1: Photon and carbon ions depth dose distributions at different energies. Photons start with a build up, which is then followed by an exponential decrease. Ions deposit most of the dose at the end of the particle track - the Bragg peak. Figure taken from [Schardt et al., 2010]

Interaction of photons with matter

Photons mostly interact with matter in one of the following ways: coherent or Rayleigh scattering, photoelectric effect, Compton scattering and pair production. The cross section σ , for each of these processes depends as well on the energy of the incident photons as on the atomic number of the absorbing material [Lilley, 2006]. The decreasing photon intensity in matter, I , can be described as:

$$I = I_0 \cdot e^{-N\sigma x} = I_0 \cdot e^{-\mu x} \quad (1.3)$$

where I_0 stands for the initial intensity of the photons, x the depth of the material in units of length, N the atomic density of the material and μ the attenuation coefficient. The cross section, σ is the sum of all possible Interaction processes:

$$\sigma = \sigma_{rayleigh} + \sigma_{photoelectric} + Z\sigma_{compton} + \sigma_{pairproduction} \quad (1.4)$$

The energy range of photons used in radiotherapy is between 100 keV and 25 MeV. The dominating process in this energy range is Compton scattering [Alpen, 1998]. The electrons resulting from Compton interaction scatter mostly in a forward direction. Therefore a maximum of the depth-dose profile occurs when electrons stop at a certain depth, the mean electron range. After this build up the dose deposition decreases exponentially (see Fig. 1.1 and Equation 1.3).

Interaction of ions with matter

Ions can interact with matter either with elastic Coloumb scattering from target nuclei (nuclear stopping) or with inelastic collision with target electrons (electronic stopping). At the ion energies used in radiotherapy, which are less then 500MeV/u, the electronic stopping is the dominating interaction. The result is ionization and excitation of the target atoms.

The mean rate of the ions energy loss in matter is described by the Bethe-Bloch formula [Bethe, 1930, Bloch, 1933]. Since we are interested in low ion energies, a non-relativistic approximation can be made:

$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi N_e z_{eff}^2}{m_e v^2} \left(\frac{e^2}{4\pi\epsilon_0} \right)^2 \left[\ln \left(\frac{2m_e v^2}{I} \right) + \text{correction} \right] \quad (1.5)$$

here N_e is the material's electron density, e and m_e are the charge and mass of an electron, ϵ_0 the electrical field constant and I the mean excitation energy of the absorber material. Barkas formula [Barkas, 1963] can be used for the approximation of the effective projectile charge z_{eff} :

$$z_{eff} = z \left(1 - e^{-125\beta z^{\frac{2}{3}}} \right) \quad (1.6)$$

where β is the projectile speed in units of c .

The energy loss of the ions is proportional to z_{eff} and inversely proportional to v^2 . The shape of the curve in Fig. 1.1 can be explained as following: Ions enter the matter with a high velocity, resulting in a small energy deposition. Their velocity gradually decreases, which in turn increases the energy deposition. The maximum of the energy loss occurs right when the ions stop and it is called Bragg peak.

Lateral scattering and range straggling of ions

As mentioned ions interact with matter mostly via electronic stopping at energies used in radiotherapy. However, nuclear stopping still occurs and it is the main reason for lateral scattering. The angular spread of ions is dependent on the mass of the target nuclei and on the momentum of the incident ions [Molière, 1948]. The lateral scattering is proportional to the mass of the target nuclei and inversely proportional to the momentum of incident ions. Carbon ions have thus less lateral scattering than protons. Experiments have shown that carbon ions have three times smaller angular spread compared to protons at the same range in water (15.6 cm, 150 MeV/u protons and 285 MeV/u ^{12}C ions) [Schardt et al., 2010].

Statistical fluctuations of specific electronic stopping events cause range straggling of ions. If the number of collisions is high or the material is thick enough these fluctuations can be approximated by a Gaussian probability distribution [Bohr, 1940, Ahlen, 1980]. The straggling width σ_R is proportional to:

$$\sigma_R \propto R/\sqrt{M} \quad (1.7)$$

where R is the mean range of ions and M the ion mass. Thus, the heavier the ion is, the less range straggling it has. Carbon ions have 3.5 smaller range straggling when compared to protons [Schardt et al., 2010].

Nuclear fragmentation

When transversing through matter ions (except protons) can be fragmented into ions with lower atomic number. The lower Z fragments travel in the same direction as projectile ions and have a significant contribution to the deposited dose (see Fig. 1.2). It is thus essential that fragments are included in the treatment planning, so that an accurate dose can be calculated.

After colliding with the target projectile fragments enter excited state. A de-excitation occurs through emission of nucleons, nucleon clusters and photons. Two of the possible fragments of projectile ^{12}C ions are isotopes ^{11}C and ^{10}C , which are both β^+ emitters [Kraft, 2000]. The resulting positron is annihilated with electrons in matter, creating two photons, which travel in opposite direction. PET (Positron Emission Tomography) can take advantage of the process without exposing patient to additional radiation.

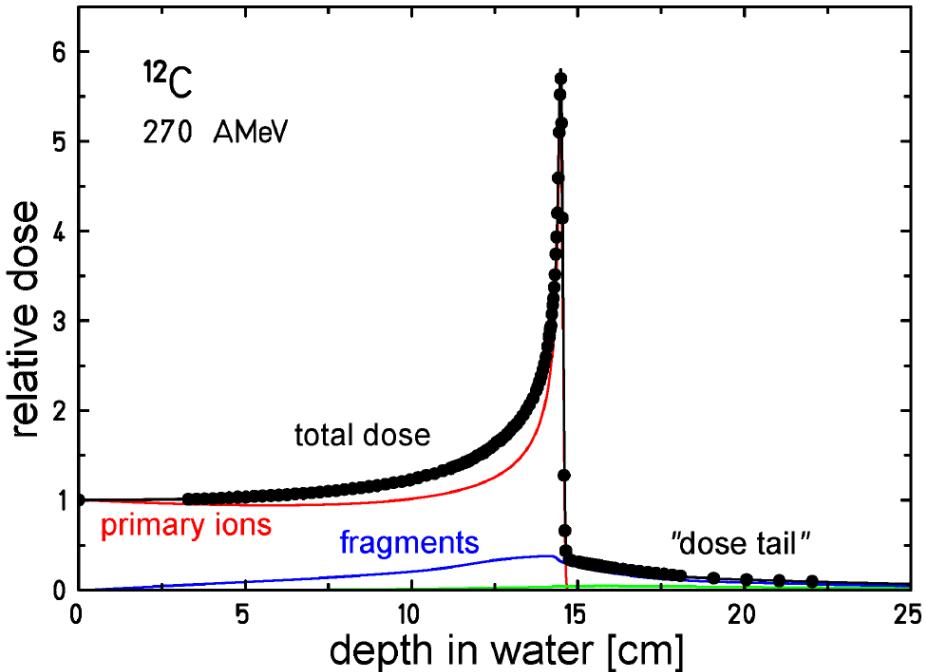


Figure 1.2: Impact of fragmentation on a depth dose distribution of carbon ions. Main contribution to the overall deposited dose (black line) comes from the primary ions (red line). The produced fragments (blue line) have a smaller impact, but non-negligible. The most profound effect is seen in the dose tail behind the Bragg peak, where dose comes only from fragments. Figure taken from [Groezinger, 2004]

Secondary electrons and track structure

Ions used in radiotherapy loose most of their energy via inelastic Coulomb scattering on target electrons. Electrons liberated from target by ions are called secondary electrons or δ -electrons. δ -electrons travel through matter, scatter further and may produce secondary ionization of the target atoms. When δ -electrons energies are larger than >50 eV, ionization becomes the dominant process, which produces a large number of additional electrons [Kraft, 2000, Schardt et al., 2010].

The radial dose profile and track diameter is defined by the energy spectrum of the δ -electrons. Most of the δ -electrons are concentrated around the projectile ions path, since they receive small energy transfers or are scattered in the direction of incident ions. Differ-

ent models [Chatterjee and Schaefer, 1976, Katz and Cucinotta, 1999] and Monte Carlo simulations [Paretzke, 1986, Krämer, 1995] predict radial dose fall-off approximately with $1/r^2$ for radial distance r . Varma et. al. have confirmed this experimentally [Varma et al., 1977]. The maximum radial distance r_{max} is defined by the most energetic δ -electrons, which are related to energy, E , of the projectile ions [Kiefer and Straaten, 1986].

$$r_{max} = E^{1.7} \quad (1.8)$$

Following equation 1.5, E is correlated to Z^2 and $1/\beta^2$, meaning that track structure is highly dependent on the projectile ion species and energy as demonstrated in Fig. 1.3: Carbon ions have much more dense ionization structure compared to protons [Krämer and Durante, 2010]. δ -electrons have low energies, and thus the r is on nanometer scale. As the energy of projectile ions decreases, their stopping power increases and causes significantly larger number of δ -electrons. The energy deposited by δ -electrons in medium is described using the Linear Energy Transfer (LET), which is closely related to dE/dx . Fast ions, with little ionization, have thus small LET, while slow ions, with large ionization, have a high LET.

1.2.2 Radiobiology

Ionizing radiation (photons and ions) causes damage throughout the cell. However the most susceptible part to radiation is the carrier of genetic information, the deoxyribonucleic acid (DNA), located in the cell nucleus [Munro, 1970]. Radiation can damage DNA directly or indirectly.

Ionization and consequent destruction of DNA molecular bonds via radiation is a direct effect (see Fig. 1.4b) and is typical for high-LET radiation. On the other hand, an indirect effect is when radiation hydrolysis water around DNA and produce highly reactive hydroxyl-radicals, OH (see Fig. 1.4a). Even though OH radicals decay fast, they are still able to cause severe damage to DNA. The formation of OH is typical for low-LET radiation like photons. The two processes, direct and indirect, are not exclusive and can damage DNA in parallel.

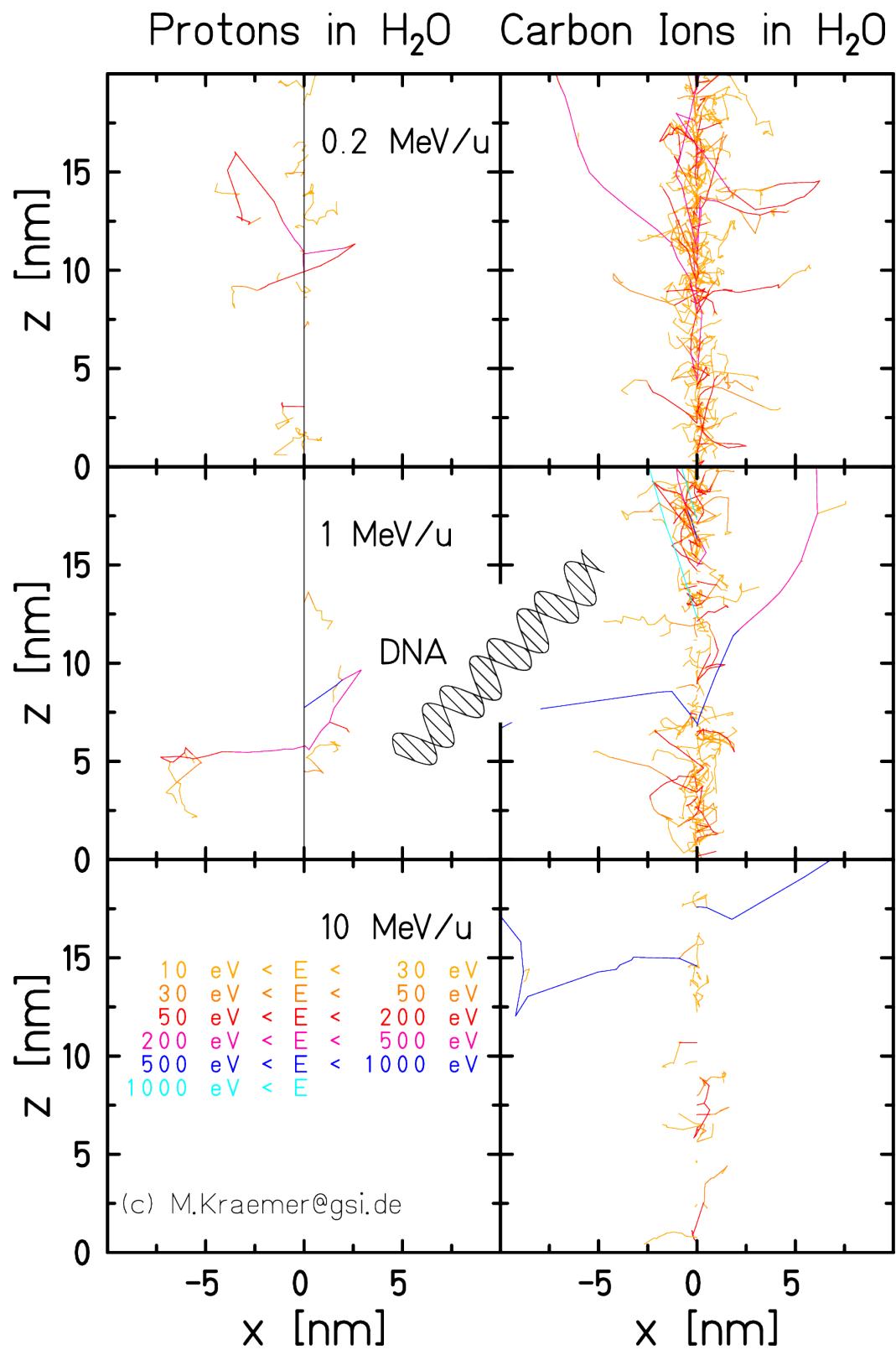


Figure 1.3: Track structure of ions in water at different energies. The distribution of δ -electrons is highly dependent on ion species and their energy. A molecule of DNA is displayed for size comparison. Figure courtesy of Michael Krämer.

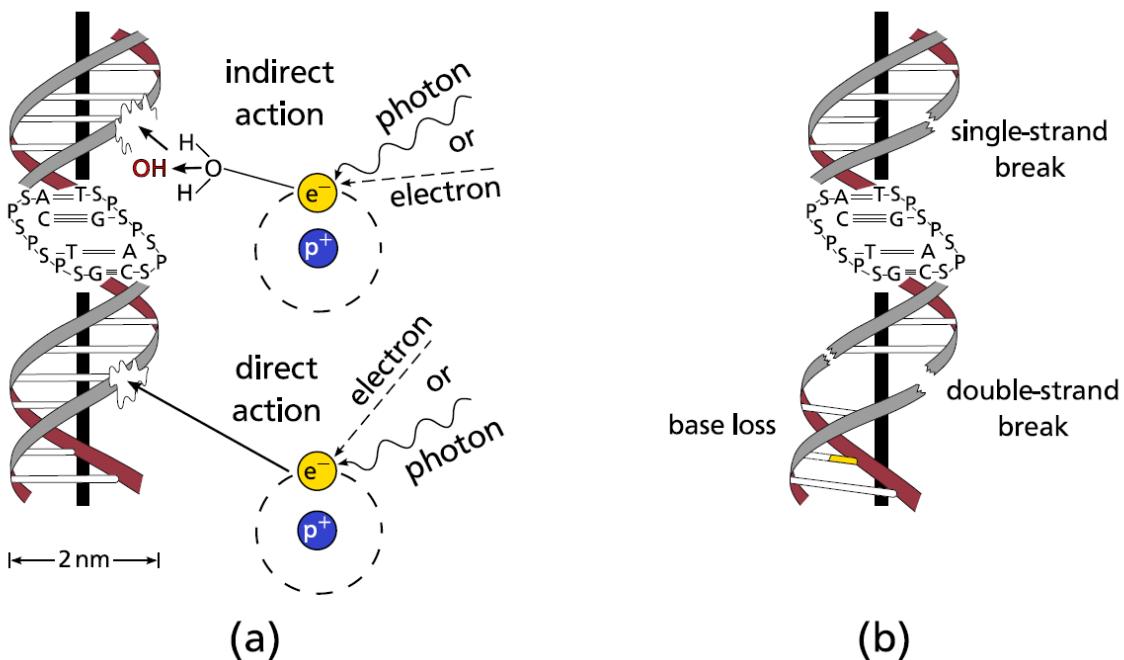


Figure 1.4: Types of DNA damage caused by radiation (a) Indirect damage occurs, when radiation forms free radicals hydroxyl radicals (OH), which can damage DNA. (b) Direct effects of radiation can cause single or double-strand breaks. Figure taken from [Richter, 2012]

Damage to DNA can result in either single strand breaks (SSB) or double strand breaks (DSB) as shown in Fig. 1.4b). When one of the double strands in the DNA helix is destroyed (SSB), it can usually be easily repaired by cell repair-mechanisms, since the complementary base is intact. If the bases on both stands are destroyed (DSB) the DNA damage is much more complex and can lead to the breakage of the chromatin. The cell repair-mechanisms can handle DSB as well, albeit not as efficient as SSB. However if there are clustered DSBs, the damage is usually too severe for repair-mechanisms to undo it. The changes in damaged DNA can lead to carcinogenesis or cell death. The aim of radiotherapy is to cause an apoptosis - a controlled self-inactivation of the cell due to the DNA damage. Beside apoptosis, cell can also undergo necrosis, an uncontrolled cell death. Cell necrosis often causes response from the immune system, leading to inflammation, which radiotherapy strives to avoid. DNA can also be damaged to such extent, that cell cannot proliferate indefinitely - a effect known as clonogenic cell death.

Relative Biological Effectiveness

Fig. 1.3 shows the size of DNA molecule in comparison with proton and carbon ion distribution of δ -electrons around their track. A clustered DSB occurs preferably around Bragg peak due to large ionization densities. Less cells will survive a clustered DSB, compared to DSB or SSB. Ions

have large ionization density and is one of the main advantages over photons in the radiotherapeutic sense. Since most of the clinical experience about cell response to radiation comes from photons, the biological effect of ions is usually described relative to a reference photon response. Relative biological effectiveness (RBE) is therefore defined as the ratio of the reference photon dose to the dose level of a specific ion radiation at the same biological effect (isoeffect):

$$RBE = \left. \frac{D_{\text{photon}}^{\text{ref}}}{D_{\text{ion}}} \right|_{\text{isoeffect}} \quad (1.9)$$

It is important to note at this point that RBE values are valid only for the same effect - the same biological endpoint and the same reference radiation. The most interesting biological endpoints in radiotherapy are cell survival and side effects. RBE values are usually obtained from cell survival curves (see Fig. 1.5). Cell survival curves, S , are commonly modeled by an exponential linear-quadratic (LQ) model [Fowler, 1989]:

$$S(D) = e^{-\alpha D - \beta D^2} \quad (1.10)$$

α is a coefficient related to a single event cell killing and β coefficient related to a double event cell killing. The ratio of α/β is a characteristic of the cell type, namely the tissue capacity to repair radiation damage. A small α/β ratio means cell is radioresistive (high repair capacity) and vice versa. As seen in Fig. 1.5 and Eq. 1.10, RBE values are dependent on the dose level. Hence in ion radiotherapy, beside the physical absorbed dose, a photo-equivalent or biological dose incorporating the RBE also plays an important role. The unit for biological dose is Gy (RBE) [ICRU, 2007].

Besides a dose level, RBE also depends on the LET, the particle species and the tissue type [Kraft, 2000]. Therefore RBE modeling is a complex topic. At GSI, RBE is calculated using the *local effect model* (LEM) developed by Scholz et al. [Scholz and Kraft, 1994]. There are two main assumptions in the LEM model. First is that localized biological effects are independent on the radiation type. Second assumption is that the photon response is the same for all dose levels (high and low). The difference between different radiation types comes from the dose deposition in a small volume in the cell nucleus. At the same total dose, many photons create a homogeneous dose distribution over a cell nucleus, while few ions cause a highly localized dose distribution around their track.

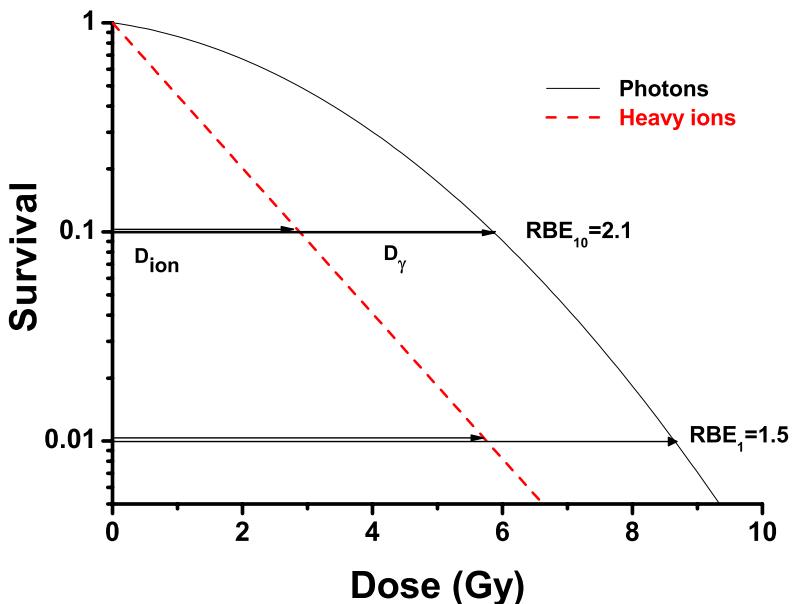


Figure 1.5: Typical cell survival curve for photons (black solid line) and heavy ions (red dashed line). Photon line shows typical shouldered form, described by linear-quadratic model. Heavy ions show a much steeper decrease with dose. The RBE value can be calculated by looking at the points at the same survival value - same biological effect. Figure taken from [Schardt et al., 2010]

LEM can thus predict dose response, by comparing photon response at the high local dose level. LEM was used clinically as well in GSI pilot project from 1998 - 2007 [Krämer et al., 2000, Krämer and Scholz, 2000] as in HIT since 2009. LEM has received several revisions [Elsaesser and Scholz, 2006, Elsaesser and Scholz, 2007, Elsaesser et al., 2009] and experimental verifications [Mitaroff et al., 1998, Krämer and Scholz, 2000, Krämer et al., 2003].

RBE for carbon ions ranges from 1 in the entrance channel, to a value around 5 at the Bragg peak [Kraft, 2000]. The highest RBE for carbon ions is right around Bragg peak, which gives carbon ions a great advantage, since there is an increased biological effectiveness at target tissue compared to the normal tissue in the entrance channel. In proton therapy a constant RBE value of 1.1 across the treatment field is used [Paganetti et al., 2002].

Fractionation

Radiotherapy applies a basic principle of radiobiology that dose fractionation spares all cell types. For a given total dose more cells will survive with dose delivered across multiple fractions, compared to a single dose, because cells will have time to repair radiation induced sub-lethal damage between fractions. With dose d delivered over n fractions, equation 1.10 can be rewritten as [Shrieve and Loeffler, 2011]

$$S = (e^{-\alpha d - \beta d^2})^n \quad (1.11)$$

The biologically effective dose (BED) is defined as:

$$BED(Gy_{\alpha/\beta}) = nd \left[1 + \frac{d}{\alpha/\beta} \right] \quad (1.12)$$

with the total dose D equal to $n \times d$, we can define fractionation factor F as

$$F = \left[1 + \frac{d}{\alpha/\beta} \right] \quad (1.13)$$

so that $BED = D \times F$. F increases with d , but decreases with α/β . Lower α/β (late-responding tissue) means higher F and a higher α/β (early responding tissue) moves F towards 1.

Hypo-fractionation

In recent years hypo-fractionation has showed promising results over wide range of tumors [Yamada et al., 2008, Greco et al., 2011, Halasz and Rockhill, 2013]. Hypo-fractionation consists of 1-3 fractions of very high doses, up to 24 Gy in a single fraction (single-dose). The theory behind hypo-fractionation is still under research and no consensus has yet been reached. On one hand, LQ model predicts higher BED for hypo-fractionation. On the other hand, Garcia-Barros et al. proposed additional mechanism at work [Garcia-Barros et al., 2003]. They presented a two target model, which suggest that tumor response to irradiation is defined not only by tumor cell type (as in LQ model) but also by micro-vascular sensitivity. With excluding targeted enzymes from knock-out mice, they showed that tumors with reduced micro-vascular endothelial apoptosis grew 200-400 % faster than a control group. The study, however, was challenged on several grounds and is controversial.

1.2.3 Application technique

The use of X-rays for treating patients has more than a century long history. There is a lot of research and practical knowledge regarding the clinical usage of X-rays. Particle therapy, on the other hand, is a more novel technique, with more patients being treated every year. In the following sections an overview will be given of how the irradiation is actually delivered to the patient for both modalities with the emphasis on ion therapy.

Photon therapy

In photon therapy high energy x-rays (MV) are used for tumor irradiation. X-rays are produced in a linear accelerator (LINAC). Electrons are accelerated with energies from 2-25 MeV and collided with a high-density target (tungsten), where x-rays are produced via bremsstrahlung. The beam is then directed to the patient and conformed to the tumor shape. The beam is shaped either by blocks at the head of the machine or by a multileaf collimator. A multileaf collimator is made of individual leaves, that can be moved to represent the tumor's shape in the beam's eye view, see Fig. 1.6.

Linear accelerators are usually placed on a gantry, which can be rotated around the patient. This allows beams to enter the patient from any angle. The arbitrary choice of beam angle is used in a 3-dimensional conformal radiotherapy, where a variable number of beams is used. Each beam is then shaped with a multileaf collimator. Even more precise technique is intensity-modulated radiotherapy (IMRT). IMRT allows treating complex tumor shapes, e.g. when the tumor is in proximity of a critical structure. Volumetric modulated arc therapy (VMAT) uses continuous irradiation together with continuous gantry rotation and multileaf collimator shaping. VMAT is able to produce even more conformal dose shapes than IMRT.

Ion therapy

In order for ion therapy be successful, ions must be accelerated to appropriate energies (several hundred MeV/u), the beam must be transported to target area and guided onto the target with the required accuracy.

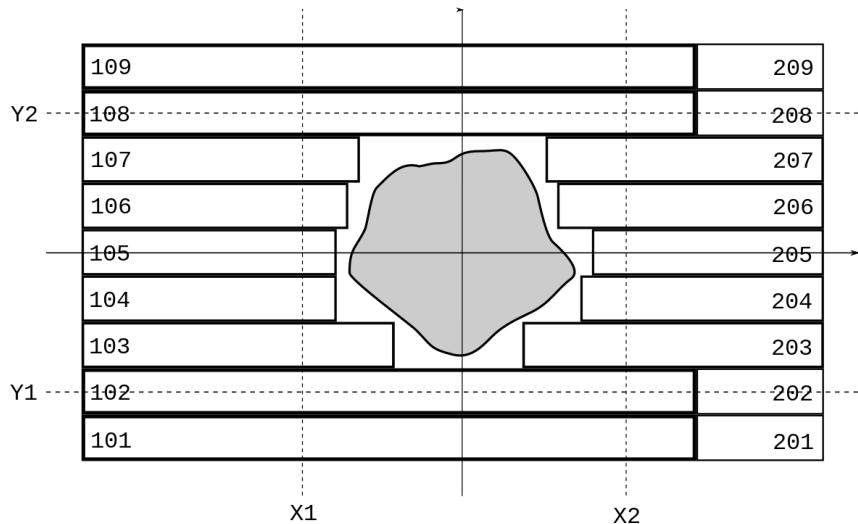


Figure 1.6: A schematic picture of a multileaf collimator. Individual leaves (marked with numbers) are positioned so that exit beam from linear accelerator conforms to the patient tumor in a beam's eye view. Picture taken from [Wikipedia, 2016].

Ion are accelerated either with cyclotrons or synchrotrons accelerators. **Cyclotrons** can be built in a compact design and offer a continuous beam with stable intensities. Cyclotrons and only be used for protons and particle energies can not be regulated and therefore passive energy degraders are needed. Active energy variation is possible with **synchrotrons**, where a linear accelerator is used to inject ions into the synchrotron and then the beam is regulated with ion optics. Synchrotrons are used in all heavy ion therapy centers, while cyclotrons are most commonly used for proton therapy.

Each tumor has a unique shape, size and position in patient. Therefore a single Bragg peak would not provide adequate dose and a beam has to be properly shaped. Two beam shaping systems are in use - passive and active beam shaping. In the next two sections both will be explained.

Passive beam shaping

The general idea of passive beam shaping is to transform a beam of a fixed single energy into the shape of the tumor. This is done in several steps as schematically shown in Fig. 1.7. Firstly, the beam is broadened using a scattering device (passive double scattering systems or magnetic wobbler) in order to obtain a broad, flat profile. In the next step, the beam is spread out over the required energy range with a range modulator. Usually a range modulator consist of rotating wheels of various thickness or a ridge filter [Chu et al., 1993]. A beam of fixed energy is thus expanded into so-called *spread-out Bragg peak (SOBP)*, which is moved to the required depth

using a range shifter. The final two devices in beam's path are built for each patient individually. Collimator shapes beam in a lateral direction, while compensator adjusts SOBP to the distal edge of the tumor. However, compensator cannot adjust dose in the proximal ledge of the tumor, resulting in an excess dose to the healthy tissue (hatched area in Fig. 1.7).

Passive beam shaping offers more robust and faster treatment delivery in contrast to active beam shaping. However, it lacks tumor conformity, the dose cannot be modulated and each patient needs individually tailored devices for each beam used in the treatment. Furthermore, the beam travels through some material, exposing patient to additional dose due to fragmentation.

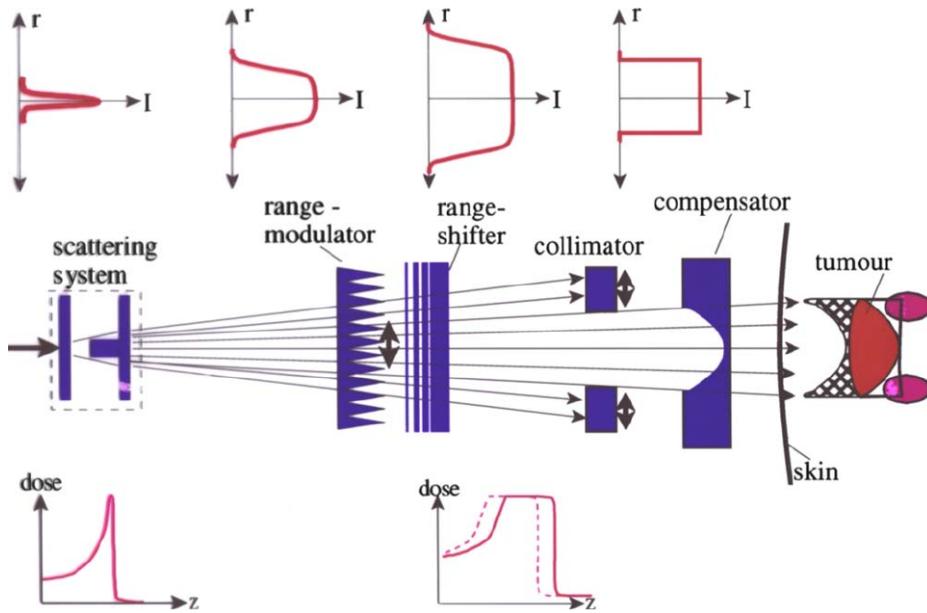


Figure 1.7: Schematic presentation of a passive beam shaping. A scattering system is used to broaden the beam. Afterwards a range modulator spreads out Bragg Peak to the required energy range. The spread out Bragg peak is then shifted to a specific energy with a range modulator. Finally, patient specific collimator and conformator serve for lateral and longitudinal conformity, respectively. The proximal edge of the tumor cannot be shaped, as shown with hatched area. Figure taken from [Schardt et al., 2010].

Active beam shaping

In contrast to passive beam shaping, active beam shaping works by dividing tumor into small points, which are then irradiated using a thin pencil beam. Tumor is first segmented into iso-energy slices (IES) and each of IES is covered with a 2 dimensional grid (raster points). A thin pencil beam is deflected from raster to raster point, irradiating each one with designated dose. The technique allows irradiation of arbitrary shape, without introducing any additional patient specific hardware. The lack of additional material in front of the patient also means less dose due to lesser neutron flux. Furthermore with the option to modulate dose in each point, dose in tumor is very conformal with less dose to healthy tissue.

There are differences in specifics of active beam shaping and the GSI system of three-dimensional scanning system will be given here [Haberer et al., 1993, Kraft, 2000, Schardt et al., 2010] and a schematic presentation is shown in Fig. 1.8 and Fig. 1.9. A synchrotron provides a thin pencil beam of ^{12}C ions with a variable energy in the range of 30 - 400 MeV/u. The energy defines the position of the Bragg peak in depth. Fig. 1.9b shows how the Bragg peaks are stacked in depth to cover longitudinal extension of the tumor. The thin pencil is guided by two magnetic deflection units to irradiate each raster point. The specific dose in each

raster point is calculated in the treatment planning. During treatment the beam stays on each raster point until intensity monitoring system measures the designated dose. Then it is moved to the next raster point. When the whole IES is irradiated, the treatment waits for the next IES comes from accelerator.

Fig. 1.9a displays how dose homogeneity in the target is achieved. To achieve flat dose distribution with Gaussian beam profile, beam's full width half maximum is three times the lateral raster spacing. Such configuration offers robustness for uncertainties of the beam spots. The spacing between individual IES is usually 3 mm, providing enough overlap between individual Bragg peaks. However, the number of IES should be kept low, since the changing of the beam energy takes most of the time and hence prolongs the treatment. Instead of using high number of IES, Bragg peaks are broadened in longitudinal direction by a using ripple filter (RiFi) - a device similar to ridge filters used in passive beam shaping.

1.2.4 Motion in radiotherapy

Patient motion can have a profound effect on the radiotherapy. It can cause large deviations from the planned dose, resulting in under- or over-dosage in target and excess dose in OAR. Motion types, its extent and origin is therefore a vast topic of research. A brief introduction will be given here, for an in-depth explanation reader is pointed to review by Langen and Jones [Langen and Jones, 2001].

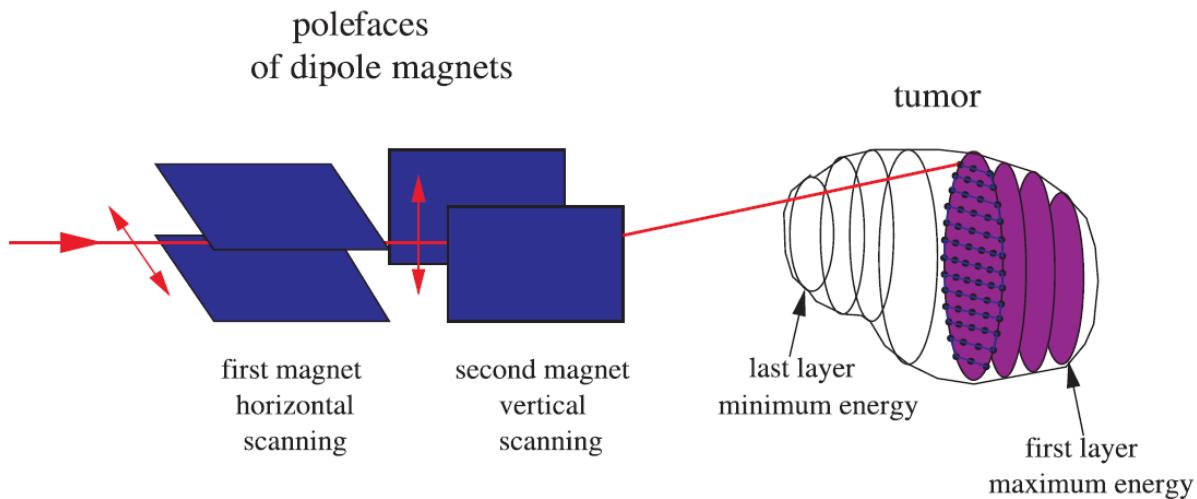


Figure 1.8: Schematics of GSI's active beam shaping. Tumor is divided into isoenergy slices, which are further overlayed with a 2 dimensional grid. Longitudinal direction (in beam's eye view) is varied with particle energy from accelerator, while lateral is via a magnetic scanning system. Figure taken from [Krämer, 2009]

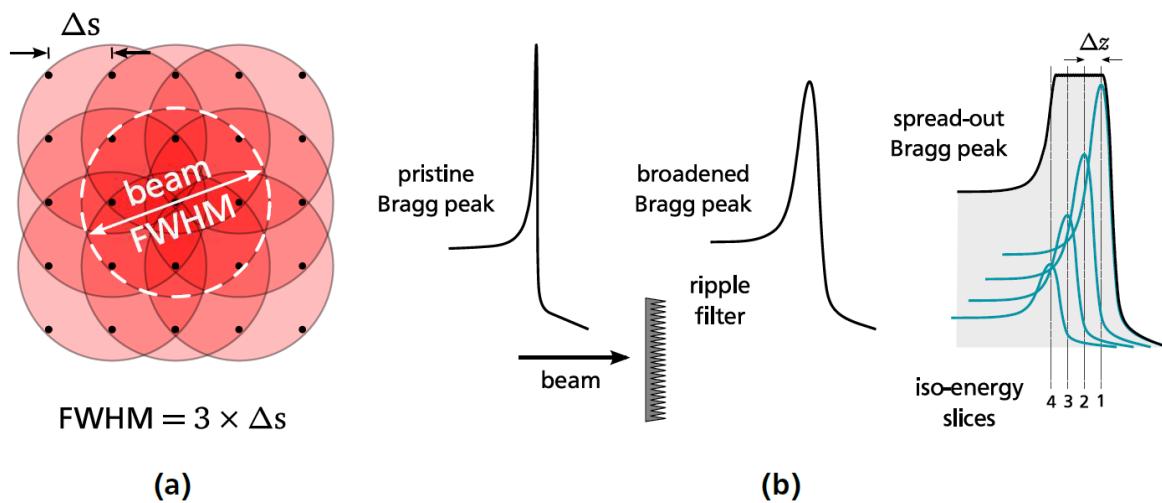


Figure 1.9: Schematic presentation of how target dose homogeneity is achieved in active beam shaping. a) To provide sufficient homogeneity in lateral direction (in beam's eye view) full width half maximum of beam is three times the spacing between raster points. b) Bragg peaks are broadened in depth with a ripple filter and then stack to provide longitudinal dose homogeneity. Figure taken from [Richter, 2012]

Motion types

There are three main types of motion: patient positioning, inter- and intra-fractional motion. All three motion types are shown in Fig. 1.10.

Patient motion is difference in patient position between image acquisition (e.g. CT) used for treatment planning and actual delivery. Patient motion introduces changes in tumor shape and tumor position. To overcome patient position uncertainties, patient immobilization and dedicated protocols are used.

Interfractional motion happens between two treatment sessions (fractions) and results in anatomical changes in a patient. It occurs on a time scale of hours and days. For lung cancer patients, tumor shrinks and lung density can change between fractions [Mori et al., 2009]. Also changes in breathing pattern can impact treatment delivery. Additionally, the tumor baseline drifts significantly [Sonke et al., 2008]. Repeated imaging and replanning reduces the impact of the interfractional motion, but requires additional time.

Intrafractional motion is mainly caused by respiration and heart beat, but also peristalsis. The time scale ranges from seconds to minutes. In this thesis we investigated treatment of lung cancer, so focus lies on respiratory motion. Respiratory motion varies from patient to patient and it is responsible for tumor motion from a mm range to a couple of cm [Shirato et al., 2004]. Tumor size and T-staging are also correlated to tumor motion [Liu et al., 2007]. The respiratory-induced motion is largest in superior-inferior (SI) direction rather than in the anterior-posterior (AP) or left-right (LR) directions [Seppenwoolde et al., 2002, Britton et al., 2007, Liu et al., 2007].

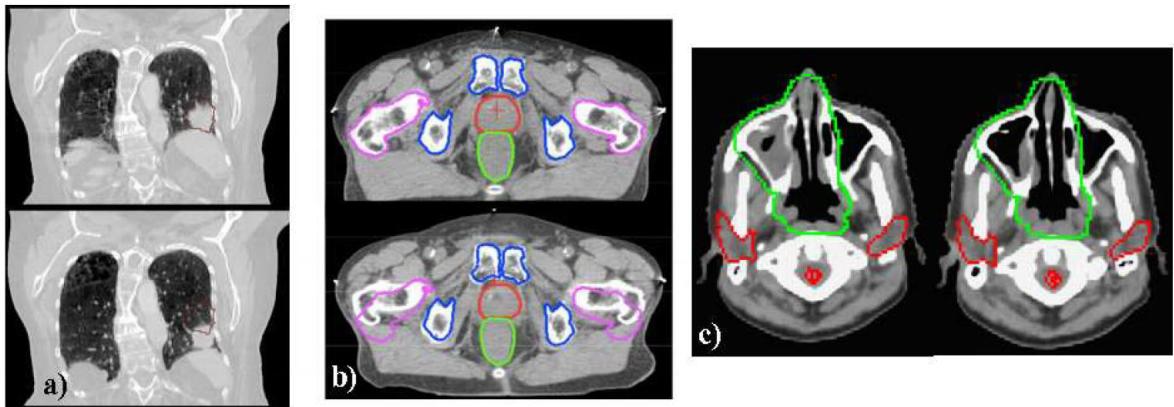


Figure 1.10: Examples of the three major motion categories. On the left side (a) a lung tumor is displayed, which moves due to the respiration of the patient (intrafractional motion). Interfractional position changes are exemplary shown in the middle (b), where two CT scans of a prostate patient are compared. Density variations between two CT scans are shown in (c). Figure taken from [Engelsman and Bert, 2011]

Motion mitigation techniques

While all three motion types have to be addressed in treatment planning, special focus will be given on intrafractional motion mitigation. Photon radiotherapy or particle radiotherapy with passive beam shaping use larger safety margins to encompass the whole tumor motion as explained in Section 1.2.5. However, larger safety margins are not enough to mitigate motion when active beam shaping is used. The beam delivery sequence and target motion interfere with one another, resulting in over- and underdosages in patients. This effect is called interplay and it has been thoroughly reviewed elsewhere [Phillips et al., 1992, Bert et al., 2008]. The effect of interplay depends on many factors, such as motion amplitude, beam direction, starting breathing phase etc. Three main techniques are currently established to counteract interplay: rescanning, gating and beam tracking. Several other techniques exist to reduce the effect of tumor motion, such as abdominal compression, jet ventilation, apneic oxygenation etc., but will not be described here, since the scope of this thesis is on free-breathing patients.

Rescanning is a technique that uses statistical averaging of different interplay patterns [Phillips et al., 1992]. Instead of applying the whole dose D at once, the target is scanned N times, each time irradiated with D/N . The result is a Gaussian dose distribution around D with no interplay (static case), as shown in Fig. 1.11. With more rescans (larger N), better dose homogeneity is achieved, because the variance is proportional to $1/N$. Technically the method is the easiest to implement of the three mentioned, since no real-time motion monitoring is necessary. The treated volume must be enlarged to at least encompass target in all motions states (in contrast to gating), which introduces additional dosage to normal tissue. Rescanning

is currently used at NIRS, Tokyo (Japan) and at *some proton centers*.

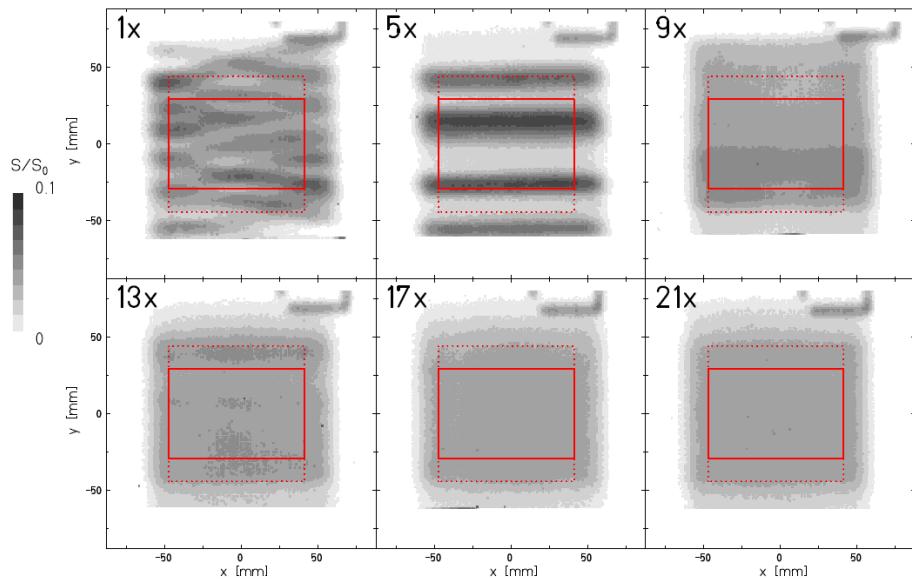


Figure 1.11: Film irradiation with rescanning. With statistical averaging of multiple interplay patterns dose in the target (solid red square) becomes homogeneous. Figure taken from [Bert et al., 2009].

Gating applies irradiation only in a selected part of the breathing cycle in a so-called gating window (GW) [Minohara et al., 2000, Lu et al., 2006a]. Usually, the end-exhale position is used as the center of the GW, as highlighted in Fig. 1.12. A motion monitoring signal is used to control beam extraction. While there is limited additional normal tissue irradiation, the treatment time is prolonged due to frequent beam interruptions as shown in Fig. 1.12. Conventional radiotherapy and passive beam shaping also employ gating to reduce the effects of motion on treatment delivery.

Beam tracking is a method where the tumor is followed by the beam throughout different motion phases in real time. Similar to gating, beam tracking is not limited to active beam shaping. It was even proposed originally for photons [Keall et al., 2001] and later implemented clinically in x-ray radiosurgery in the robotic Cyberknife Synchrony system (Accuray Inc., Sunnyvale, Ca., USA) [Brown et al., 2007, Kilby et al., 2010]. Regardless of radiation type, a fast beam delivery system is required for beam tracking. In contrast to photon radiotherapy, beam tracking with particles need to pay special consideration to range changes. At GSI beam tracking system has been implemented. The solution for fast longitudinal range changes was carried out by two polymethyl methacrylate (PMMA) wedges close to the target, that are operated via linear stepmotor [Saito et al., 2009], as shown in Fig. 1.13. The stepmotor can change the relative distance between the wedges and therefore introduces more or less material the beam travels through and consequently changes the effective beam energy (range). The beam posi-

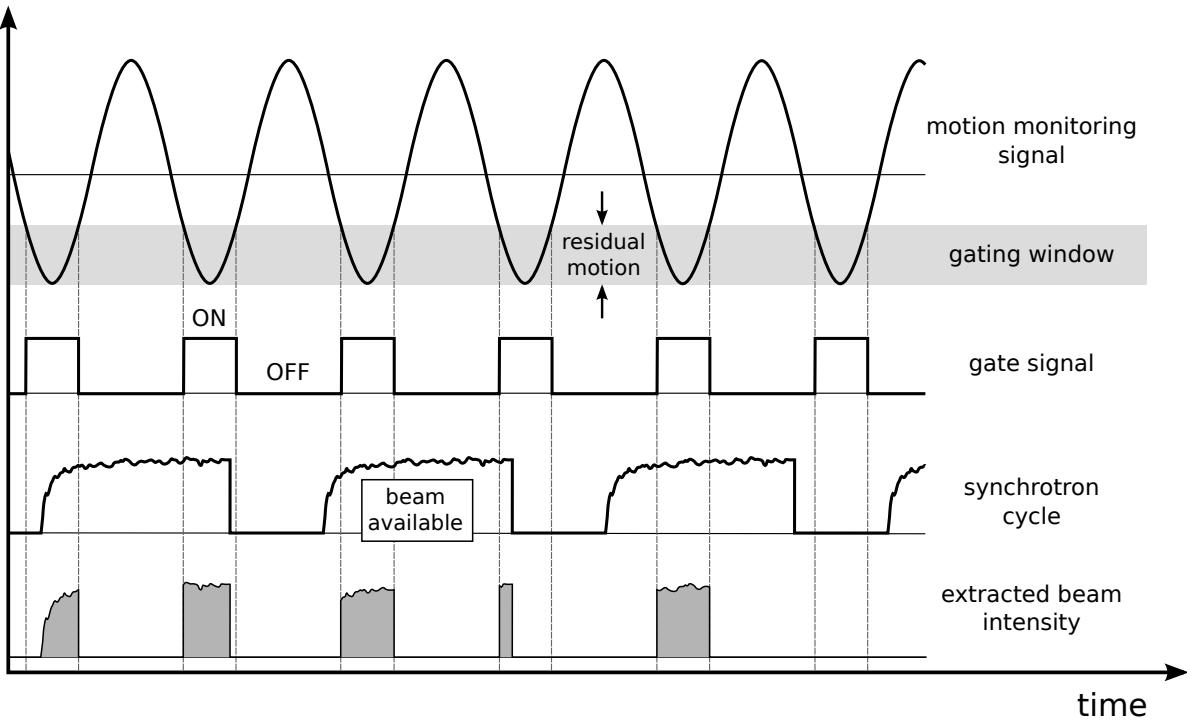


Figure 1.12: Gating delivery with a synchrotron accelerator. The irradiation is only possible, when the gate signal is active and the beam is available. The gate signal depends on gating window and motion monitoring signal. Figure taken from [Richter, 2012].

tion is corrected according to the motion monitoring signal and pre-calculated look-up tables for the required compensation parameters. The beam tracking system at GSI is able to achieve high precision [Bert and Rietzel, 2007, Bert et al., 2009, Saito et al., 2009]. Clinical implementation, however, is not yet feasible due to several reasons, such as the precision and speed of the motion monitoring, the ion-beam tracking system complexity and inverse interplay.

The three motion mitigation techniques mentioned are not exclusive and can be used in parallel. Furukawa et al. made a study on a combination between rescanning and gating [Furukawa et al., 2007] and Water et al. presented a combination between rescanning and tracking [van de Water et al., 2009].

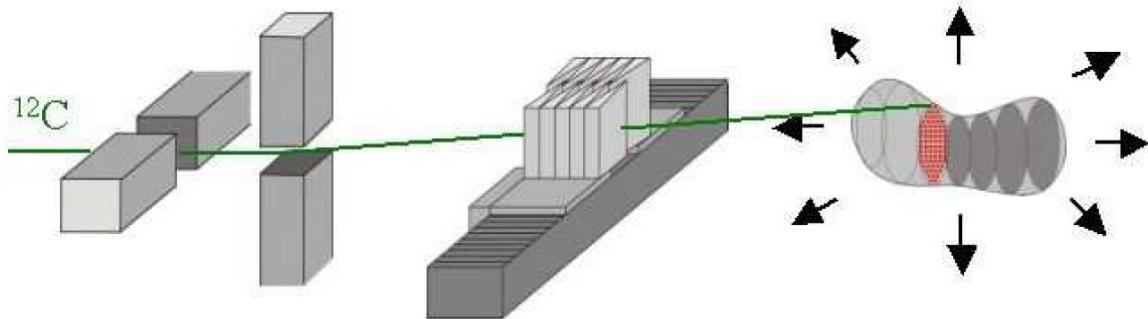


Figure 1.13: Schematic presentation of GSI's beam tracking system. Two PMMA wedges, mounted on linear steppers, can change the energy of the beam traveling through. The changes in lateral direction are achieved via dipole scanner magnets. For the longitudinal adaptation two PMMA wedges are mounted on step motors, enabling to change the depth the particle beam has to traverse. Figure taken from [Groezinger, 2004]

1.2.5 Treatment planning

The task of treatment planning is to determine machine parameters in order to deliver prescribed dose to the target, while not violating maximum allowed dose to critical organs, also known as organs at risk (OARs) [Richter, 2012]. Treatment planning thus revolves around dose optimization process and it is highly dependent on delivery type used for treatment. The optimization problem for tumors can be written as:

$$\min_x \sum_i (f(x, A_i) - D_{pre})^2 \quad (1.14)$$

Here i is a CT voxel, function f is a dose deposition model, x intensity of the radiation beams, A patient geometry and beam parameters and D_{pre} is the prescribed dose.

The basis of treatment planning is a computed tomography (CT), where target volume and OARs are delineated done by physician. Additional imaging, such as magnetic resonance (MRI) or positron emission tomography (PET), is often used as a supplement to CT for enhanced contrast of it. In the following sections, the target definition will be explained and the basics of scanned ion beam treatment planning. Afterwards an explanation on dose calculation for moving targets will be given.

Target definition

The definition of the target volume is crucial, since it has to cover the whole tumor, prevent further tumor spreading, while at the same time it should not be too big to spare normal tissue.

The International Commission on Radiation Units (ICRU) recommends the following definitions for volumes used in treatment planning, which will also be used in this work, see Fig. 1.14 [ICRU, 1993a, ICRU, 1999].

Gross Tumor volume: *The GTV is the gross palpable or visible/demonstrable extent and location of malignant growth.*

Clinical Target Volume: *The CTV is a tissue volume that contains a demonstrable GTV and/or sub-clinical microscopic malignant disease, which has to be eliminated. This volume thus has to be treated adequately in order to achieve the aim of therapy, cure or palliation.*

Planning Target Volume: *The PTV is a geometrical concept, and it is defined to select an appropriate beam size and beam arrangements, taking into consideration the net effect of all the possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV.*

Internal Target Volume: *This is the margin that must be added to the CTV to compensate for expected physio-logical movements and variations in size, shape, and position of the CTV during therapy.*

Organs at risk: *Organs at risk (OAR) are normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose.*

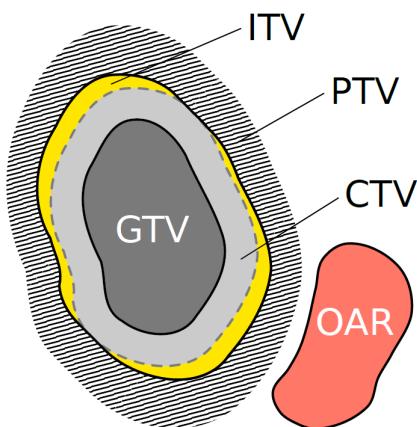


Figure 1.14: ICRU treatment planning volumes definitions. Figure taken from [Richter, 2012]

Further recommendations of the ICRU state that 100% of the PTV volume should receive between 95% and 100% of the planned dose [ICRU, 1993a].

Treatment planning for scanned ion beams

A treatment planning system (TPS) for active shaping ion beams has to model the active beam delivery system and the beam interactions with the tissue. Furthermore, for ions heavier than protons the biological effectiveness and fragmentation must also be considered, which add additional complexity to the TPS. A TPS for beam scanning was developed at GSI, called TRiP98. The basic concepts of TRiP98 will be presented here, further reading can be found elsewhere [Krämer et al., 2000, Krämer and Scholz, 2000, Richter et al., 2013].

TRiP98 divides PTV into energy slices, which are further divided into raster points in a defined order that the beam will follow. In the optimization step, a gradient-decent algorithm iteratively optimizes particle number for each raster point, so that the optimal target dose is achieved. Dose can either be physical or biological, using LEM biological effectiveness (see Section 1.2.2). Physical characteristic of the beam include lateral scattering as proposed by Molière [Molière, 1948] and nuclear fragmentation that yield secondary particles. The patient specific geometry and tissue inhomogeneities are accounted for using a transformation from CT HU to water-equivalent path length (WEPL) [Geiss et al., 1999, Jäkel et al., 2001, Rietzel et al., 2007].

GSI's 4D treatment planning system

As mentioned in section 1.2.4 tumor motion can cause severe dosimetric errors. To asses dose deficiencies and to overcome them, TRiP98 was expanded to be able to calculate time-resolved (4D) treatment plans. The new software was named TRiP4D and a detailed description is given by Richter et al [Richter et al., 2013].

A static CT is not sufficient for 4D treatment planning. Time-resolved CT scans (4D-CT) therefore have to be used. 4D-CT consist of several quasi-stationary sections, called motion phases. Data is recorded in each slice throughout the whole motion and is then sorted to appropriate motion phases, according to motion signal [Rietzel et al., 2005a].

Besides a 4D-CT, a vital part of 4D treatment planning is **image registration**. It provides quantification of motion with deformation maps between different 4D-CT motion states. Image registration principles are described in Section 1.2.5. The image registration is not included in TRiP4D, so an external software must provide the necessary deformation maps.

The calculation of 4D dose starts with the division of the treatment plan into sub-plans, according to the motion phase it will irradiate. The number of sub-plans is the same as number of motion phases (or number of motion phases in gating window, if gating is used). Afterwards the number of particles is calculated in each voxel of all of the motion phases used. Finally, the particle number in each voxel is transformed with the deformation maps obtained from registration, to the reference phase, where the accumulated dose from summed particle numbers is calculated (see Fig. 1.15). If biological dose is calculated, then instead beside particle numbers,

energy spectra is also accumulated, so that the RBE can be calculated according to LEM for the total dose to each CT voxel.

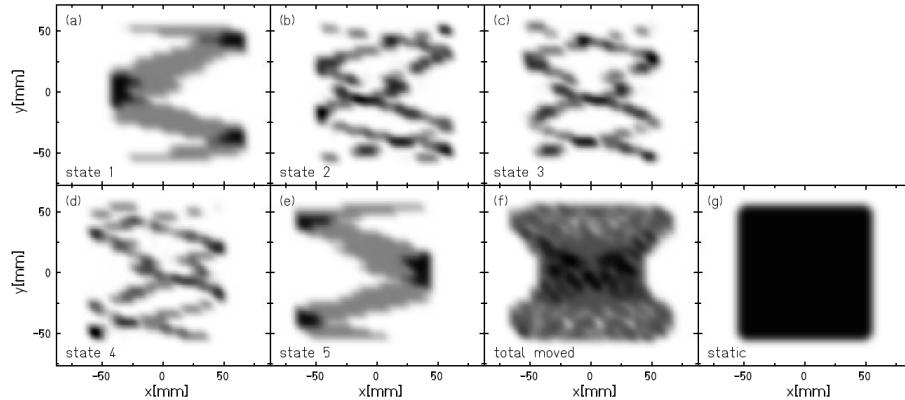


Figure 1.15: Experimental validation of TRiP4D dose calculation on film response. On images a)-e) the individual dose deposition for the five motion states is showed. Image f) shows accumulated 4D dose and image g) a homogeneous dose on a stationary film. Figure taken from [Richter, 2012]

Image registration

Temporal changes in patient anatomy are assessed with image registration. Registration can be made between different imaging modalities (CT, MRI, PET), between scans from different days or between different phases in 4D-CT. It requires two images: a fixed and a moving one. The result of the registration is a deformation map originating from the moving and pointing to the fixed image. Registration can be written as:

$$x' = x + u_{ri}(x) \quad (1.15)$$

Here, x and x' are points in states r and i , respectively and u_{ri} is a vector field representation of the transformation map. u_{ri} can be used to assess motion amplitude, propagate contours and calculate 4D dose. It is important to note that certain steps in 4D treatment planning require also inverse registration, from state i to r [Richter, 2012]. If deformation map is applied to the moving image, the new image is called warped image and it should be as close to the fixed image as possible. Fixed, moving and warped image are shown in Fig. 1.16.

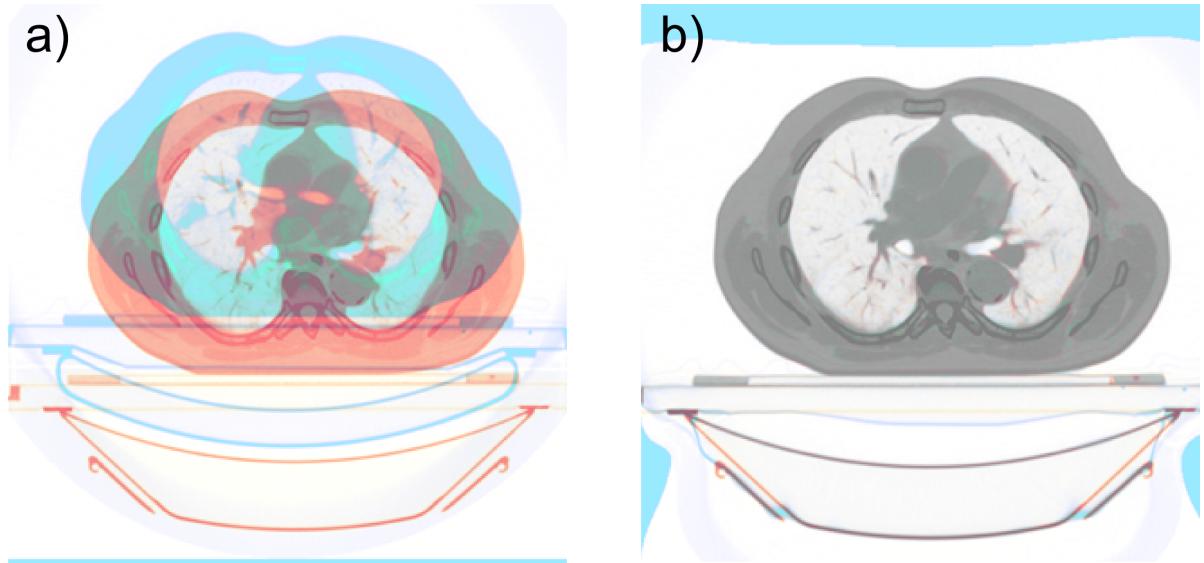


Figure 1.16: Overlap of fixed and moving image CT scan (a) and fixed and warped image after registration (b). Inverse colors are used in both CTs so that the overlaid image should be gray where the images overlap perfectly.

There are different possible types of registration and can be placed in two groups. First group consist of linear registrations: translation, rotation and scaling. In medical imaging the most commonly used linear transformation is translation or rigid registration. The other group of registrations are elastic or deformable registrations. The actual algorithms for performing registration are complex and the reader can find detailed review elsewhere [Hill et al., 2001, Brock et al., 2006, Rietzel and Chen, 2006]. A multi-institutional study has shown that the accuracy for the majority of the algorithms is in the order of image voxel size, i.e. millimeters [Brock, 2010]. The study further states that the registration quality depends on image contrast. The quality of image registration is actually hard to quantitatively asses and usually the registration results are checked visually. To improve image registration quality assurance a dedicated software was developed and is described in detail in chapter **REF**.

1.3 Lung cancer

There were 1.8 million new lung cancer cases diagnosed worldwide in 2012 [WCRF, 2016]. With a very poor prognosis (5-year survival rates in Germany are 16% for men and 21% for women [Kaatsch et al., 2014]) lung cancer is one of the most frequent and most deadly cancer types. Usually lung cancer is distinguished into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Around 14% of lung cancer cases are SCLC [Tsao, 2016], which is normally treated with chemotherapy and radiotherapy, while for NSCLC the traditional course of treatment are surgery and radiotherapy. An example of cancerous lung tissue is shown in Fig. 1.17.

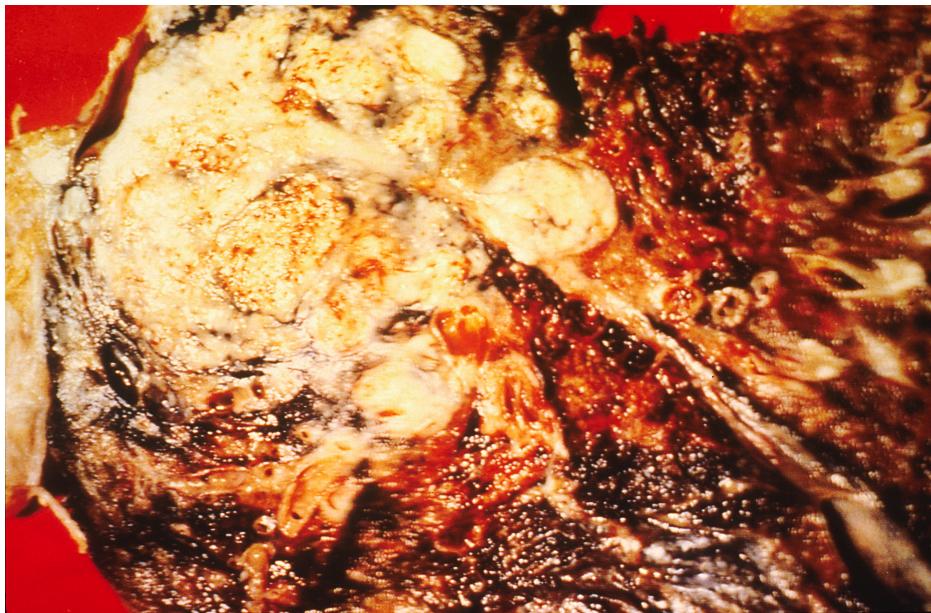


Figure 1.17: Cross section of a human lung. The white area in the upper lobe is cancer, the black areas indicate the patient was a smoker. Figure taken from [NCI, 1988]

1.3.1 Epidemiology

The main cause for lung cancer is a long-term exposure to tobacco smoke [Tsao, 2016], with 85% of cases contributed to smoking. There are over 70 known carcinogens in cigarette smoke, such as benzo[a]pyrene, 1,3-butadiene and a radioactive isotope of polonium, polonium-210 [Hecht, 2012]. See Fig. 1.18 for correlation between sales of tobacco products and rate of the lung cancer.

Studies have shown that passive smokers have an increased risk of lung cancer as well, with more than 20% increase in risk for those who live with someone who smokes and 16-19% increase for someone working with a smoker [Taylor et al., 2007]. There is some controversy

whether smoking cannabis increases risk of lung cancer - two reviews from 2013 and 2014 have found contradicting results [Tashkin, 2013, Underner et al., 2014].

The other 15% of lung cancer cases is attributed to a combination of genetic factors, exposure to radon gas, asbestos or other forms of air pollution [J. and M., 2010].

20-Year Lag Time Between Smoking and Lung Cancer

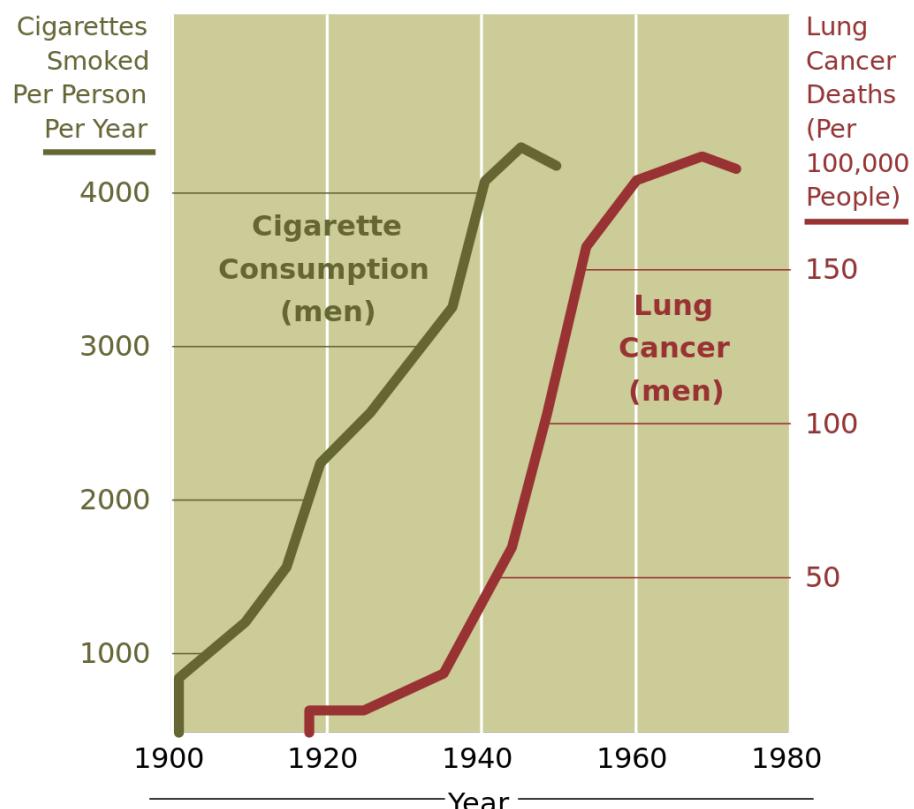


Figure 1.18: Correlation between sales of tobacco products and the rate of the lung cancer in the USA between 1900 - 1970. Data released from National Cancer Institute.

1.3.2 Non-small cell lung cancer

The NSCLC is divided into three main groups: adenocarcinoma, squamous-cell carcinoma and large-cell (undifferentiated) carcinoma [Kasper et al., 2015]. Between 25-35% of all lung cancer cases are adenocarcinoma, squamous-cell carcinoma contributes to around 30% of lung cases and 10-15% are large-cell carcinoma. The SCLC contributes the rest.

Lung cancer staging is used to refer to the extent to which the lung cancer has to spread from its original source. Additionally, staging is used to establish treatment and prognosis [Chheang and Brown, 2013]. For NSCLC, the TNM classification is used, which depends on size of the primary tumor (T), involvement of the lymph node (N) and distant metastasis (M) [Kasper et al., 2015]. According to the TNM class a group is assigned, from stage 0, IA, IB, IIA,

IIB, IIIA, IIIB to IV. A schematic presentation of some stages is shown on Fig. 1.19. Prognosis is highly dependent on stage, as shown in Table 1.1.

Table 1.1: Five-year survival rates for different stage of NSCLC. Data taken from [Rami-Porta et al., 2009]

Clinical stage	Five-year survival (%)
IA	50
IB	47
IIA	36
IIB	26
IIIA	19
IIIB	7
IV	2

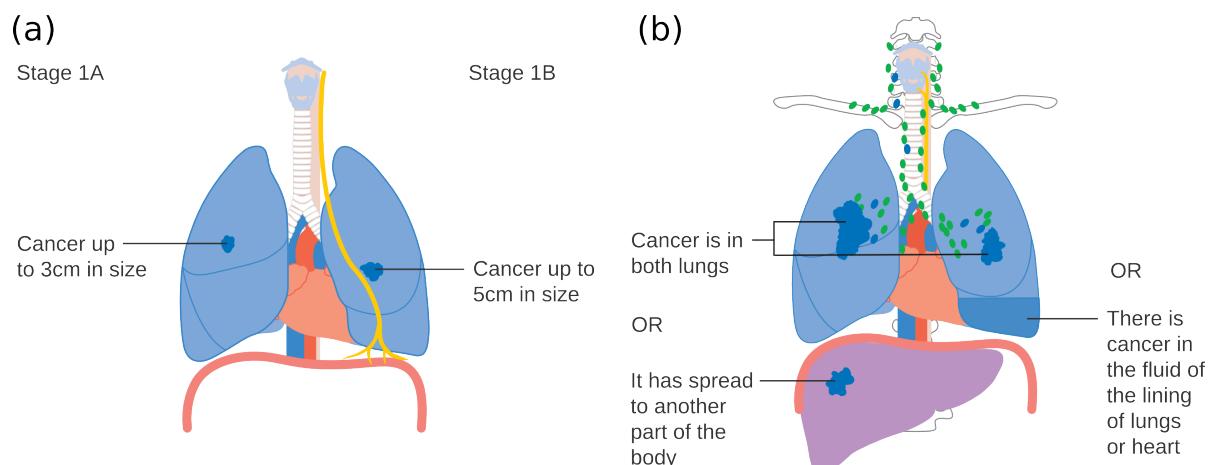


Figure 1.19: Schematic presentation of three NSCLC stages. (a) Stages IA and IB; (b) Stage IV.
Figure taken from [CRUK, 2016]

Treatment

The treatment for NSCLC can consist of surgery, chemotherapy, radiation therapy, or a combination of modalities. The treatment course depends on tumor type and stage and on patient overall condition. The typical treatment is surgery for stage I and II disease [Tsao, 2016]. Surgery resection consist of either lobectomy or pneumonectomy, together with sampling lymph node or even a complete lymph node dissection. Surgery will only be performed if NSCLC patients have enough lung reserve after lobe or lung is removed. The 5-year survival rate for NSCLC patients undergoing surgery is about 55 to 70% and 35-55% for stage I and II disease, respectively.

For unresectable stage III lung cancer the treatment consist of either chemotherapy or radiation therapy or a combination of both. The median survival for patients with unresectable stage

IIIA disease is 10-14 months [Tsao, 2016]. For all treated stage IIIB disease the median survival is 7-15 months [K. et al., 2005].

Rather than treating stage IV disease, palliation of symptoms is the goal. With chemotherapy, targeted drugs and radiation therapy the tumor burden can be lessened and the quality of life can be improved. The prognosis is poor, with median survival only 9 months and less than 25% survive the first year after the disease is diagnosed [Tsao, 2016]. Recent phase II trial combined chemotherapy with stereotactic body radiation therapy and showed promising results with 20 months overall survival [Iyengar et al., 2014].



2 Deformable Image Registration and Validation

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2.1 Introduction

Most modern clinics today regularly use different imaging techniques including CT, 4D-CT, cone-beam CT, MRI and PET. Registration is needed to overlay different image acquisitions, such as image taken at different days or between imaging modalities or to quantify anatomical changes in a time-resolved image acquisition (4D-CT). While most commercial treatment planning software provide rigid registration between different images, deformable image registration (DIR) is currently rarely used. DIR can quantify anatomical and biological variations better compared to rigid registration [Sarrut, 2006]. It opens exciting new options in radiotherapy, such as 4D optimization [Trofimov et al., 2005], 4D dose calculation [Flampouri et al., 2006] or contour propagation [Lu et al., 2006b]. 4D dose calculation has been well established for photons [Ong et al., 2016], protons [Paganetti et al., 2005] and carbon-ions [Gummel et al., 2011] and has received several experimental verifications [Vinogradskiy et al., 2009, Perrin et al., 2016, Bert et al., 2012b]. 4D dose calculation requires DIR for deformation of dose distributions in each motion state to the reference phase, where the dose from all motion states is accumulated. Special consideration has to be paid for calculation of biological 4D doses [Gummel et al., 2011]. Contour propagation can be done

with DIR [Lu et al., 2006c, Rietzel et al., 2005b] or with deformable model driven techniques [McInerney and Terzopoulos, 1996, Montagnat and Delingette, 2005], which uses a physical model to iteratively match the contour to image features. 4D dose calculation is usually more complex, since it depends on tissue density, alpha-beta ratio and it requires accurate DIR at every voxel, whereas contour propagation needs accurate DIR at contour boundaries. Besides radiotherapy, DIR usage spreads even into other categories [Cleary and Peters, 2010, Herrell et al., 2012, Nithiananthan et al., 2011, Naini et al., 2010]. Several different DIR algorithms are available, such as B-spline [Rueckert et al., 1999], Demons [Thirion, 1998], linear elastic finite element [Venugopal et al., 2005], optical flow [Zhong et al., 2007] or viscous fluid [Christensen et al., 1996].

One of the reasons why DIR is not used in commercial software is the lack of proper DIR quality assurance (DIRQA). While several different DIRQA methods exist, none of them are definitive and most of them are time consuming. It is possible to evaluate DIR with deformable phantoms, where the type and size of deformation is known [Kashani et al., 2007, Kirby et al., 2011]. However this effort is prohibitive in everyday clinical work flow. DIR validation can also be based on landmark positions, specifically their location before and after registration. In absence of externally planted markers, locating landmarks in patient anatomy can be time-consuming and it can be difficult to identify landmarks in low-contrast regions [Varadhan et al., 2013]. Another option is to compare delineated contours with the propagated ones with dice similarity coefficient [Varadhan et al., 2013] or Hausdorff distance [Huttenlocher et al., 1993]. It is more efficient technique than landmark checks, however it requires additional delineation and it does not address the region within the contour.

A set of tools were created to systematically handle DIR and DIRQA. Tools were constructed for the open-source software 3D Slicer. A presentation will be given on how DIR was calculated with the existing software. Furthermore, new DIRQA tool will be presented. It is an extensive tool, with several different checks, to assess DIR. Finally, DIR and DIRQA tools were tested on a large data set and results will be presented in the Section 2.3.

2.2 Implementation

2.2.1 3D Slicer

3D Slicer (Slicer) is a software platform for analysis and visualization of medical images [Slicer, 2016a, Fedorov et al., 2012]. Slicer is a free, open-source software (BSD-style license) available on Windows, MacOSX and Linux operating systems. It comes with a vast variety of tools, such as:

- Handling of a variety of image formats, including DICOM, NRRD and MHA
- Visualization of voxel images, polygonal meshes and volume renderings
- Image registration (rigid and non-rigid) and display of vector fields
- Automatic image segmentation
- Analysis and visualization of diffusion tensor image data
- Device tracking for image-guided procedures

The source code of Slicer is written in C++ and it's wrapped with Python to provide rapid, iterative development. The graphical user interface is based on Qt. Visualization is based on VTK, a graphical library commonly used in scientific research.

Slicer is a research tool and as such allows implementation of new functionalities in the form of extensions (modules). They can either be as external command-line programs, as scripts to automate Slicer processes or as unique modules with new features. In the next sections, different Slicer modules will be presented, which were all developed in the scope of this thesis. The purpose of these modules is to perform DIR and provide validation of the obtained results.

Registration nomenclature

To provide a clear and consistent description of methods used, an overview of the expressions is given here.

- **Reference image** - image that serves as a reference position in registration (image that is registered to).
- **Moving image** - image that is matched to the reference image (image that is registered from).
- **Warped image** - result of applying a transformation map from registration to the moving image. It should be as close to the reference image as possible.

- **True registration** - registration from moving to reference image. Similar, everything connected to true registration will use “true” (true vector field, true warped image, true absolute difference, true Jacobian, etc.).
- **Inverse registration** - registration from reference to moving image (opposite or inverse of true registration). As in true registration, the term inverse can be used for everything connected to it (inverse vector field, inverse warped image, inverse absolute difference, inverse Jacobian, etc.).

In radiotherapy true registration is used for dose propagation and consequential 4D Dose calculation, whereas with inverse registration contours can be propagated from reference to moving phase.

2.2.2 Registration

Plastimatch [Shackleford et al., 2010] is a commonly used software for registration in medical research. It is a free and open-source software, available as a command-line executable program. Plastimatch B-spline registration is also available in Slicer as part of an extension SlicerRT [Pinter et al., 2012]. The integration of Plastimatch in Slicer brings the advantage of a graphical user interface and hence a quick modification of parameters and display of results. However, for a large number of registration an automatic process is needed. For a complete 4D-CT registration there are $2(N - 1)$ registrations required - from reference phase to each of N phases of 4D-CT and vice versa, except for the reference phase itself. Typical 4D-CTs consist of 10 phases, therefore a automatic registration of a 4D-CT is a necessity.

Automatic DIR was achieved with a Python class to handle image locations, store DIR parameters, to perform DIR in the Plastimatch module, to use correct naming conventions and to store all output files (vector fields and warped images). The Python class is shown in Appendix ??.

2.2.3 Registration Quality Checks

In order to provide visual and quantitative assessment of the registration quality a **Deformable Image Registration Quality Assurance** module was created. It provides different image checks (inverse color, checkerboard, absolute difference, flicker, movie and landmark positions) and vector checks (Jacobian and inverse consistency error). Details on all different checks will be explained in this section. Reference and warped image, true and inverse vector are used as inputs for DIRQA module. Additionally, landmarks and region of interest (ROI) can also be used as an input.

Absolute difference, Jacobian and inverse consistency error were build using tools from the ITK library [Yoo et al., 2002].

Inverse color

Overlaying two different images will highlight the difference between them. However, since CT scans are usually displayed in grayscale color code, the differences can be indistinguishable. Especially if the images are quite similar, as reference and warped image should be. With applying opposite color codes to overlaying images two things are achieved. First, regions where the registration was successful will be in grayscale. And second, the differences between images will be in the color of the image they originate from. In the module we used red and cyan color code for reference and warped image, respectively. See Fig. 2.1 for details.

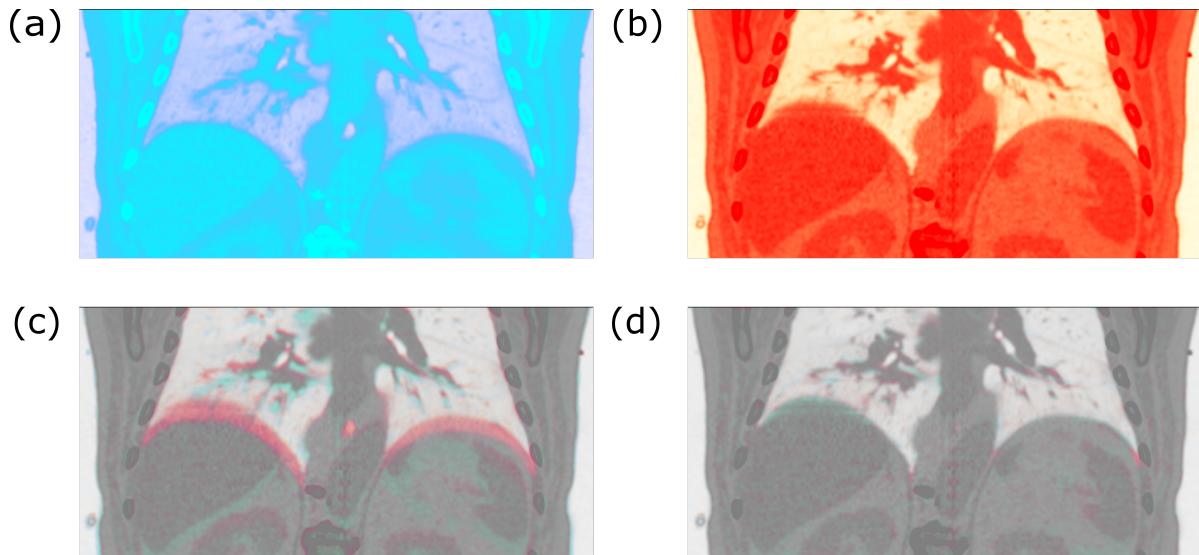


Figure 2.1: Example of a inverse color overlay. Images (a) and (b) show red and cyan color code, respectively, for a CT scan. (c) displays overlaid inverse colored images before and (d) after registration.

Checkerboard

As the name suggests, checkerboard creates an image of tiles. Each tile alternates between reference and warped image, as shown in Fig. 2.2. The differences between two images become apparent if there is no smooth transition from one tile to the next. The number of tiles can be manually selected. While the checkerboard offers clear indication of differences, it requires a user to spot them.

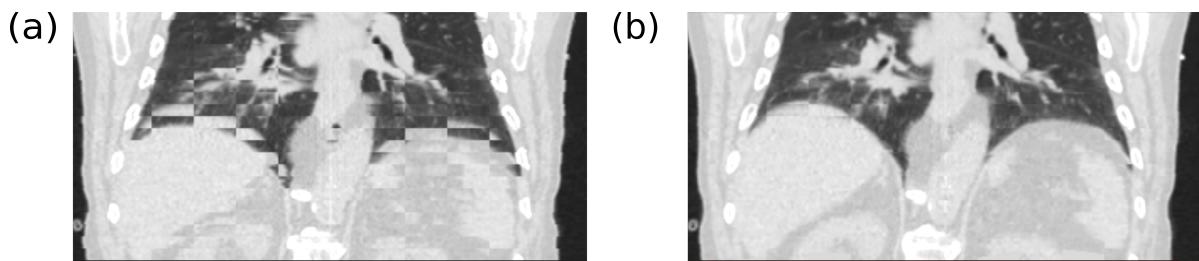


Figure 2.2: Example of a checkerboard image. It consists of tiles alternating between two images. Tiles in image (a) alternate between scans before registration and in image (b) after registration.

Absolute difference

To stress the difference between reference and warped image an absolute difference between voxel values is calculated and displayed. A new image is generated with voxels populated as the

absolute difference between reference and warped image voxel values, as shown in Fig. 2.3. Furthermore, statistical values of absolute differences are calculated (mean, standard deviation, minimum and maximum) for quantitative assessment of registration quality (in the ideal case all values would be 0).

Three absolute differences can be calculated: between reference and moving image, called default absolute difference; between true warped and reference image, called true absolute difference; between inverse and moving image, called inverse absolute difference. Usually, registration works on minimizing absolute difference (mean square error metric), so it is a direct indicator of registration success.

To spare computational time or to focus on a specific region, absolute difference can also be calculated just on a specific ROI (if used as an input). Usually the patient body is selected as ROI, without air and couch.

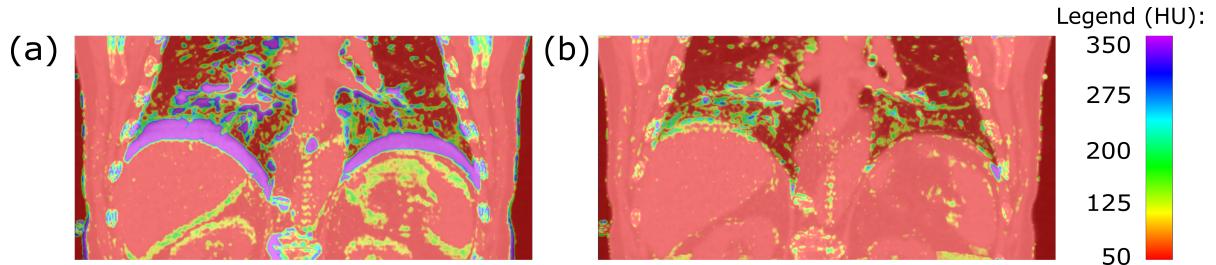


Figure 2.3: Absolute difference image before (a) and after registration (b). The mean absolute difference before registration (default absolute difference) is 62 HU and 31 HU after registration (true absolute difference).

Movie

Medical images are usually quite large - typical CT image consist of $512 \times 512 \times 100$ pixels, which makes inspecting image checks (inverse color, checkerboard, absolute difference) a time-consuming task. Movie feature allows for smoother display of different image slices. User selects which view he would like to inspect (axial, sagittal or coronal) and presses start. Selected views then start scrolling from one limit to the other. It allows user to focus on registration details, rather than scrolling through slices.

Movie and flicker (explained in the next section) do not offer any specific registration checks, but improve the process of DIRQA.

Flicker

While it is possible to display two images side by side in Slicer, it can sometimes be hard to see fine differences between the two images. Flicker alternates between reference and warped image on a single display at a 0.5 s rate.

Landmark distances

Distances between landmark before and after registration are often used to determine registration spatial accuracy [Castillo et al., 2009]. Landmarks can either be a specific feature in patient anatomy or an external marker. The position of landmarks in the warped image would ideally be at the same position as in reference image. The module measures the Euclidean norm between the landmark positions in reference and warped image.

User has to manually select landmarks in reference and moving image. For landmarks based on patient anatomy a selection from physician is required. Landmarks from moving image can then be automatically transformed to warped image with registration vector field or they can be manually selected in warped image itself. An example is shown in Fig. 2.4.

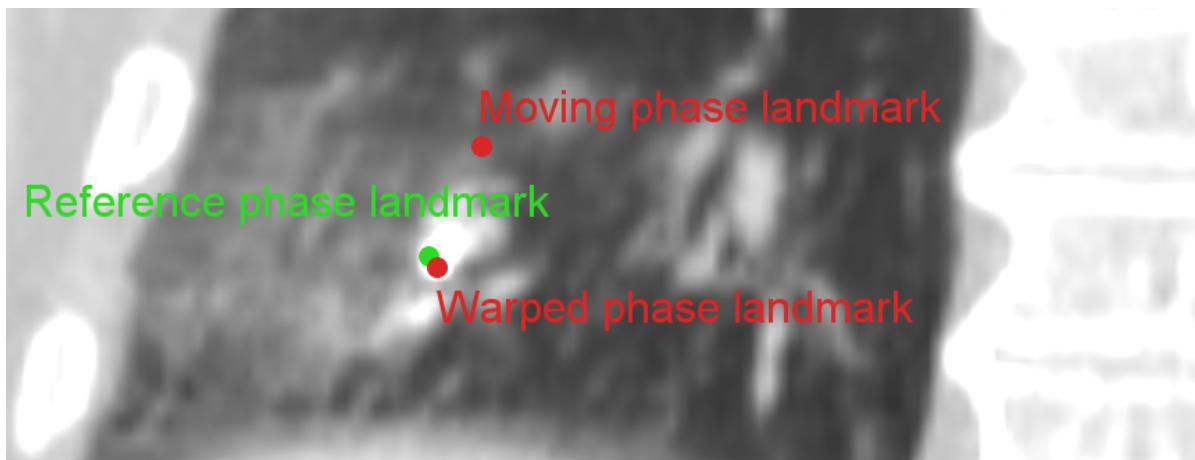


Figure 2.4: Display of landmarks in three phases - reference, moving and warped phase. Distance before registration (between reference and moving landmark) is 22 mm and after registration (between reference and warped landmark) is 2 mm.

Jacobian determinant

The Jacobian determinant or Jacobian (J) of the vector field u is calculated as:

$$J = \begin{vmatrix} \frac{\partial u_x}{\partial x} & \frac{\partial u_x}{\partial y} & \frac{\partial u_x}{\partial z} \\ \frac{\partial u_y}{\partial x} & \frac{\partial u_y}{\partial y} & \frac{\partial u_y}{\partial z} \\ \frac{\partial u_z}{\partial x} & \frac{\partial u_z}{\partial y} & \frac{\partial u_z}{\partial z} \end{vmatrix} \quad (2.1)$$

The Jacobian is used to validate physical behavior of the registration [Leow et al., 2007]. The Jacobian of vector field should be positive, since negative Jacobian values correspond to organ folding, which is physically unrealistic for patient anatomy [Rey et al., 2002, Chen et al., 2008]. Expansions and contractions around a point are indicated by Jacobian values of greater and less than 1, respectively.

DIRQA module calculates and displays the Jacobian of the vector field, as shown in Fig. 2.5. Statistical values of Jacobian are also calculated. Similar to absolute difference, Jacobian can be calculated inside a ROI rather than on a whole image.

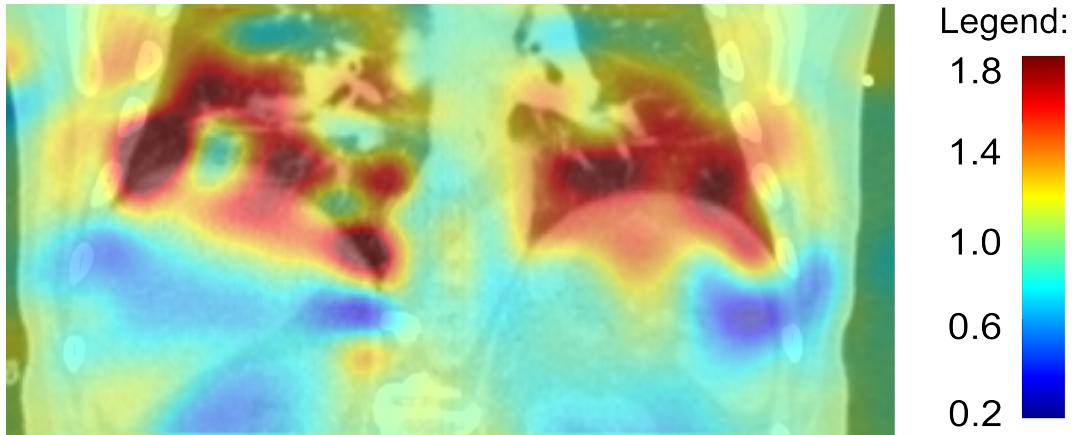


Figure 2.5: Image of Jacobian overlaid on a CT scan. The average value of the displayed Jacobian is 0.98 with 0.09 standard deviation.

Inverse Consistency Error

Inverse consistency error (ICE) is consistently used in literature as one of the main vector field checks [Christensen and Johnson, 2001, Bender and Tomé, 2009]. The principle is as follows. Suppose we have two vector fields: u_{AB} obtained from registration of image A to B and u_{BA} from registration of image B to A . The two registrations should be preformed separately. In an ideal scenario, u_{AB} would be a direct inverse of u_{BA} . However, DIR algorithms do not yield perfectly

inverse consistent vector fields. Therefore, the differences between true and inverse vector fields have to be examined.

To check for ICE, an algorithm was created that first transforms a point x in image A, using u_{AB} . The newly obtained point x' is then transformed with the inverse vector field, u_{BA} which yields x'' . The ICE is defined as Euclidean norm between x and x'' :

$$ICE = |x - x''| = |x - u_{BA}(x')| = |x - u_{BA}(u_{AB}(x))| \quad (2.2)$$

Points x' and x'' can have an arbitrary position in space, while vector fields u_{AB} and u_{BA} are positioned on a grid. To apply transformation $u_{BA}(x')$, x' is interpolated on a u_{BA} grid. A tri-linear interpolation is used in this module.

As in Jacobian, ICE image is calculated and displayed, along with statistical values and ROI feature. An example is shown in Fig. 2.6.

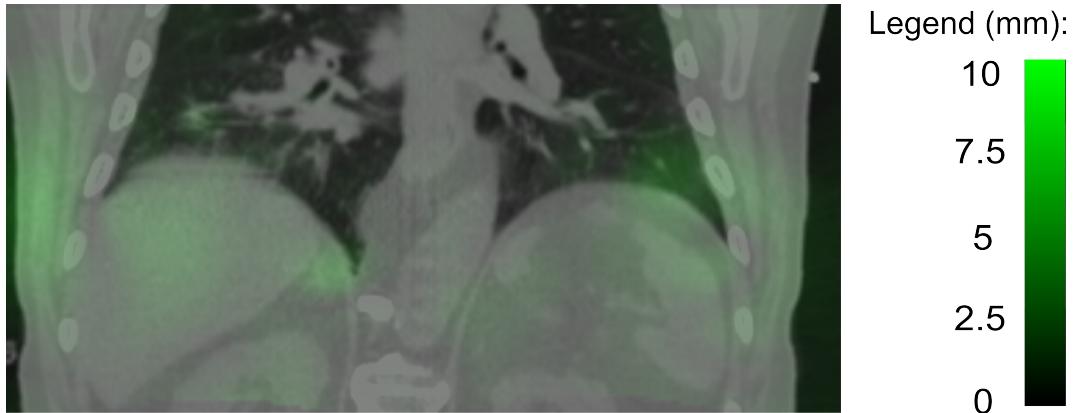


Figure 2.6: Image of the inverse consistency error (ICE) overlayed on a CT scan. The average value of displayed ICE is 1.0 mm with 0.8 mm standard deviation.

2.3 Verification

Several extensions for Slicer were created to perform DIR and DIRQA. All extensions have to undergo testing to prove their functionalities. Furthermore it is necessary to verify if extensions could be used in a typical clinical work flow. Especially DIRQA, which could facilitate the transition of DIR in everyday clinical work flow.

DIR and DIRQA were done on lung 4D-CT patient data. As part of an animal study [Lehmann et al., 2015a] DIR and DIRQA were integrated in a simulated clinical work flow.

2.3.1 Registration of lung 4D-CT patient data

Chapters **REF** and **REF** present studies on simulating active scanning carbon ion treatment (CiT) for non-small cell lung cancer patients. The effects of interplay can drastically change the dose distribution for CiT and it is necessary to quantify the effects of motion with DIR and transfer results into treatment planning software (TRIP4D in our case). An automatic procedure is required to perform DIR and DIRQA on a large number of patients. This was achieved with Slicer modules described in Section 2.2.

Materials and Methods

A time-resolved CT (4D-CT), consisting of 10 motion phases (0 - 9) with approx. 1 mm pixel and 2 mm slice spacing was acquired with either Philips Brilliance BigBore 16-slice (Philips Healthcare, Eindhoven, Netherlands) or a Philips Gemini PET-CT 16-slice scanner. Phase 0 and 5 correspond to the max end-inhale and max end-exhale breathing state, respectively. Phase 0 was chosen as a reference phase. 23 4D-CTs of lung cancer patients were used in this study.

True and inverse DIR were done for each patient between each phase and the reference phase. Each 4D-CT had 18 DIRs, leading to 414 DIRs in total.

B-Spline Plastimatch module in Slicer was used for DIR (see Section 2.2.2). DIRs were done in two stages with details given in Table 2.1.

Table 2.1: Parameters used for B-Spline Plastimatch DIR. A mean squared error metric was used. Details for each parameter can be found in [Plastimatch, 2016].

Parameter	Stage 1	Stage 2
Resolution	4,4,2	1,1,1
Grid size	50	15
Regularization lambda	0.005	0.005
Iterations	200	100

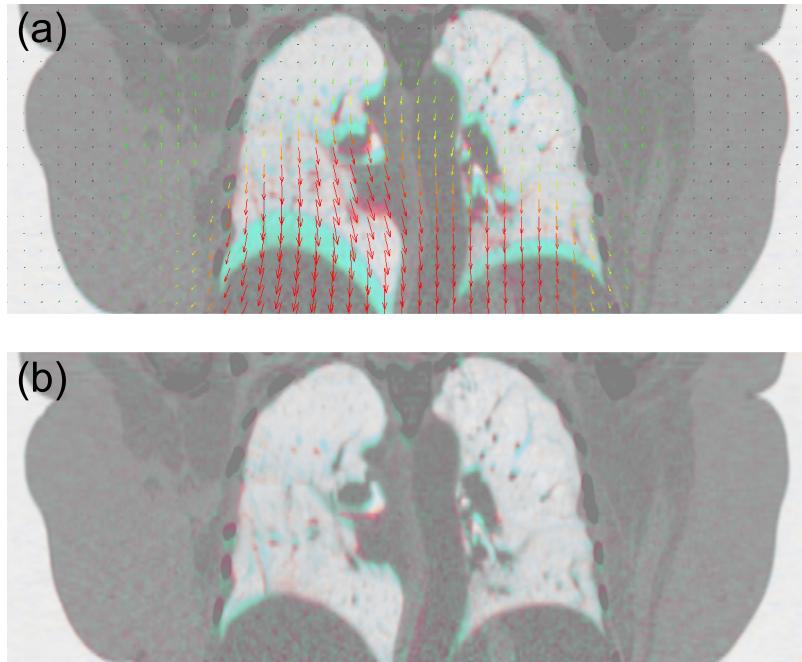


Figure 2.7: Inverse color overlay of two phases before (a) and after (b) DIR. Vector field is displayed on image (a) as arrows.

A ROI around patient body was manually created in Slicer by visually inspecting each reference phase of a 4D-CT. The ROI was then used for calculation of absolute difference, Jacobian and ICE.

Default, true and inverse absolute difference were calculated (see Section 2.2.3). In total 621 absolute differences were calculated. All images were down-sampled by a factor of 2 before calculation to save computer time. Similarly, 414 vector fields were down-sampled by a factor of 2 before calculating Jacobian and ICE. Jacobian and ICE checks were calculated on all vector fields. Additionally, each vector field magnitudes were analyzed for mean, standard deviation (STD) and maximum (max) values. Paired t-tests were performed to compare statistical values of true and inverse vector field magnitudes. A p-value < 0.05 was considered significant.

For each patient it took around 20 min for all 18 DIR and around 30 min for complete DIRQA on the 18 DIR. A Linux computer with 8 central process units cores (CPU) and 32 GB RAM was used for DIR and DIRQA.

Results

An example of DIR is displayed in Fig. 2.7. Vector fields statistical analysis is shown in Table 2.2. There was no statistical difference between true and inverse vector field magnitudes. The biggest contribution to vector field magnitude was from superior-inferior direction (around 50%), followed by anterior-posterior direction (around 30%) by left-right direction (around 20%).

Table 2.2: Data of vector magnitudes. Values are presented as mean (range).

	True vector field	Inverse vector field
Mean	0.38 (0.01 - 1.28)	0.38 (0.01 - 1.3)
STD	0.95 (0.04 - 3.17)	0.98 (0.04 - 3.55)
Max	9.67 (0.61 - 28.56)	10.17 (0.56 - 37.11)

True and inverse absolute difference dependence on default absolute difference is shown in Fig. 2.8. It also shows default absolute difference distribution across 9 phases.

Distribution of true and inverse Jacobian and ICE data are displayed in Fig. 2.9.

True and inverse maximum and minimum Jacobian and maximum ICE values were plotted against maximum vector magnitudes and fitted with linear function. Results are shown in Fig. 2.10.

All linear fits used in Fig. 2.8 and 2.10 were statistically significant ($p < 0.05$).

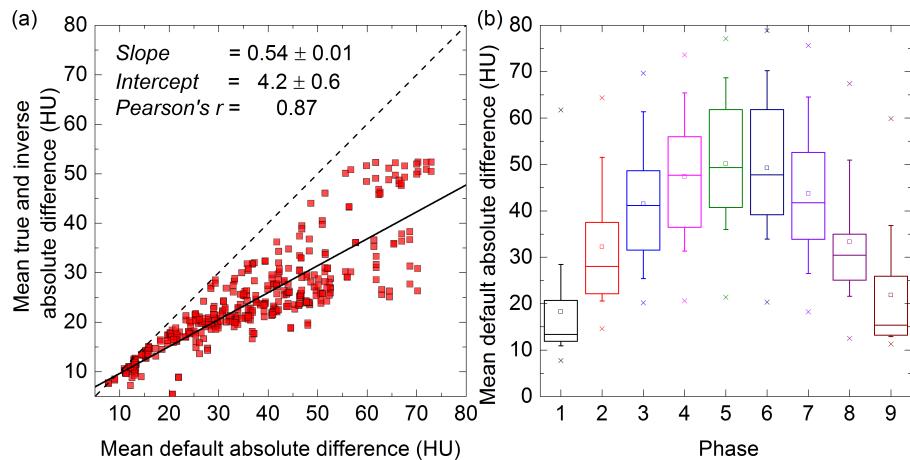


Figure 2.8: (a) Mean true and inverse absolute difference plotted against mean default absolute difference. Solid line shows linear fit, with parameters written in corner. Dashed line shows $y(x) = x$. (b) Box plots of mean default absolute difference distribution across nine 4D-CT phases. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

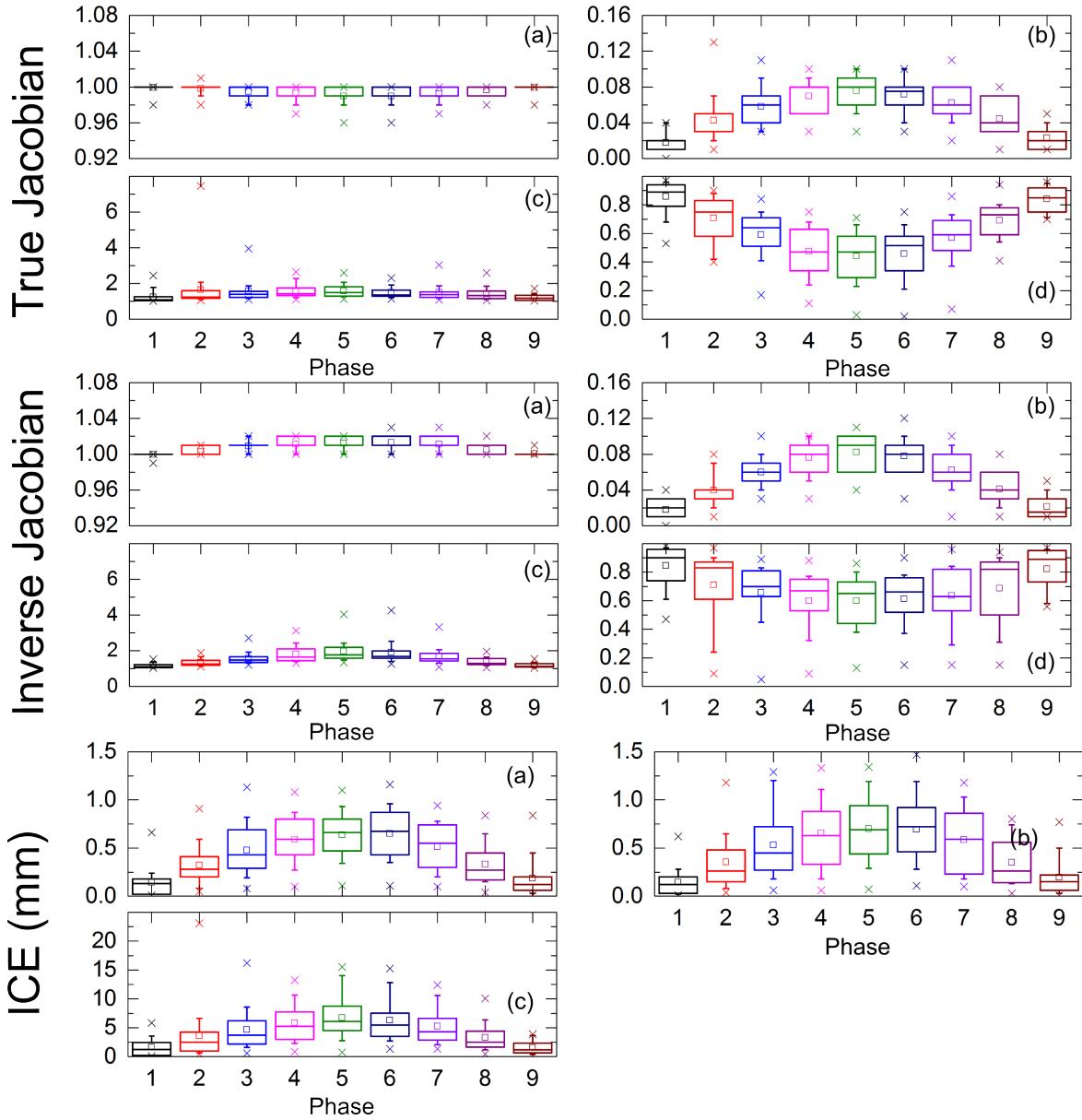


Figure 2.9: Data for true (top) and inverse (middle) Jacobian and ICE (bottom) for 9 4D-CT phases (reference phase 0 is excluded) for 23 lung cancer patients. Mean, STD, maximum and minimum are represented as (a), (b), (c) and (d), respectively. Minimum ICE is 0 throughout all phases and patients. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

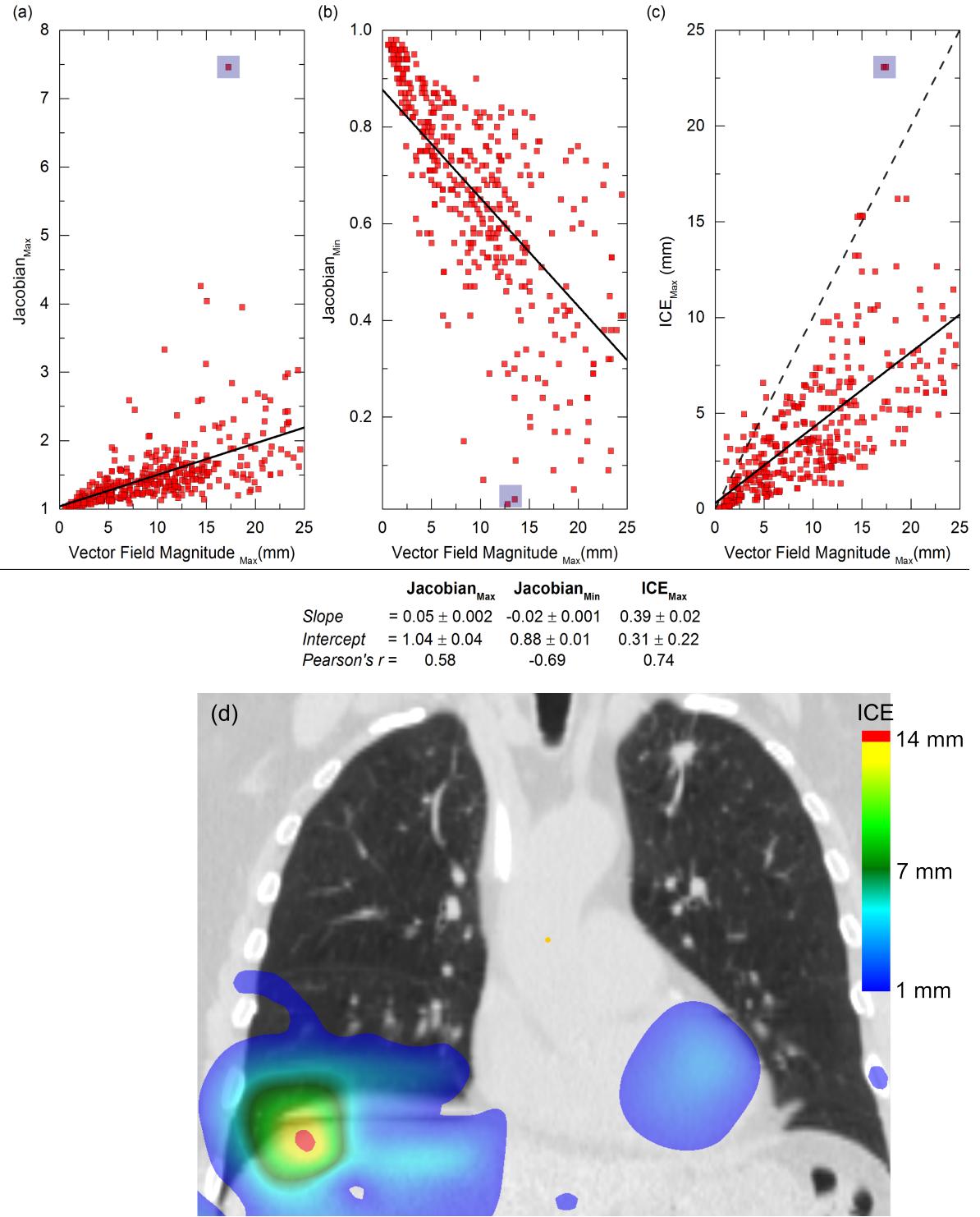


Figure 2.10: Values of maximum Jacobian (a), minimum Jacobian (b) and maximum ICE (c) plotted against maximum vector magnitudes. Linear fit is displayed with solid line and parameters are written below the plots. Dashed line in (c) shows $y(x) = x$ plot. ICE on image (d) is taken from patient highlighted with blue squares in (a)-(c). ICE is displayed using color table as displayed in legend.

Discussion

A DIR was successfully made for 23 4D-CTs, producing 414 true and inverse vector fields. All 414 DIR underwent a DIRQA consisting of vector field magnitudes, absolute difference, Jacobian and ICE.

Vector field magnitudes confirm previously published data that the biggest motion for lungs is in superior-inferior direction [Seppenwoolde et al., 2002, Britton et al., 2007, Liu et al., 2007]. The mean vector field magnitude is small (in submillimeter range), because the ROI included the whole patient body, not just the lungs where most of the motion occurs. Vectors and inverse vectors are similar, which was expected.

There was a good correlation (Pearson's $r = 0.87$) between absolute difference before and after DIR. The slope of lineare fit suggests, that B-Spline DIR on average halves the absolute difference. However, there are several outliers from the linear fit for default absolute difference bigger than 50 HU. All absolute differences after the DIR are smaller then before, which is a necessary condition in order for DIR to be considered successful.

Due to small mean vector field magnitudes, average values for true and inverse Jacobian were 1 ± 0.05 , which indicates that most of the patient body does not change during the 4D-CT scan. However, patient expansions and contractions can be seen on maximum and minimum Jacobian, with average values around 1.50 and 0.65 respectively.

Mean and STD ICE are in submillimeter range, due to the correlation between vector field and ICE (see Eq. 2.2). The maximum ICE (2.3 cm) was observed in a patient with an artifact present in the state 2 of 4D-CT, as shown in Fig. 2.10. but still smaller as average maximum vector values.

Large vector field magnitudes will produce more errors in DIR as shown in Fig 2.10. Linear fit was used to estimate increase (decrease) of Jacobian and ICE. As a rough DIRQA check, ICE should always be smaller than maximum vector field magnitudes. To confirm this, all cases above dashed line in Fig 2.10c were investigated and were found to have areas of poor DIR. An extreme case (highlighted in Fig. 2.10a-c) had a large image artifact present in phases 2 and 3 (phase 3 with ICE is shown in Fig. 2.10d) leading to large inconsistencies in DIR. The effect of DIR inconsistency on contour propagation can be seen in Fig. 2.11, where lungs and liver contour were propagated using DIR. The propagated contours clearly differ from the image features.

The 4D-CT DIR investagated here were used in particle therapy treatment planning. All areas that were found to have a poor DIR, were so far away from the target, that it did not effect contour propagation of 4D dose calculation and hence a repetition of DIR was not necessary. I. e. the patient in Fig. 2.11 had a tumor in the upper left lung lobe and DIR inconsistencies were found in lower right lung lobe. Therefore all DIRs were considered successful. It should be

stressed, however, that in this study only 4D-CTs that had a good contrast and no image artifacts in tumor vicinity were used. For a fair comparision, random 4D-CTs should be used.

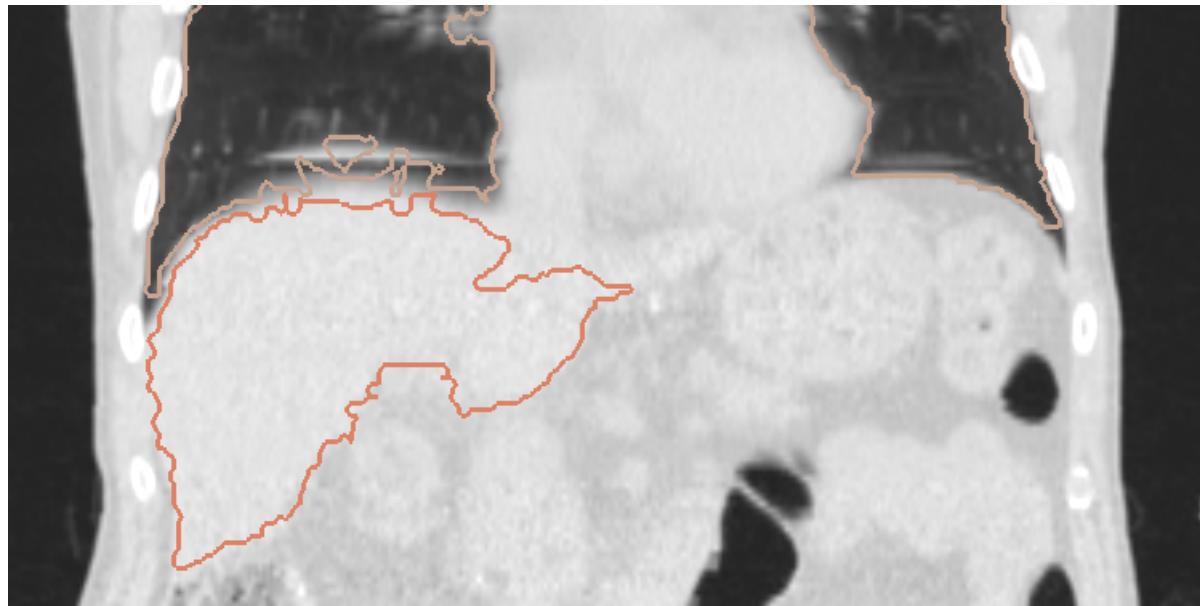


Figure 2.11: Example of a contour propagation with a inconsistent DIR. Lungs are outlined in brown and liver in red.

2.3.2 Registration of pig heart 4D-CT data

Atrial fibrillation is the most common type of cardiac arrhythmia, causing a quivering motion of the heart. In itself it is not a life threatening, however it worsens the patients quality of life and increases the risk of a stroke [Benjamin et al., 1998]. A common method for treating atrial fibrillation is catheter ablation [January et al., 2014], where the success rate is still limited and can even lead to major complications or even death of a patient [Cappato et al., 2005, Cappato et al., 2010].

As an alternative treatment, a carbon-ion therapy was proposed [Bert et al., 2012a] and later feasibility on a beating heart was shown experimentally [Lehmann et al., 2015b]. In 2014 a pilot experiment was performed at GSI using large animal model (pigs) and scanned carbon-ion to verify the treatment *in vivo* [Lehmann et al., 2015a].

To estimate and compensate motion of the heart during irradiation DIR of 4D-CT data was required. Furthermore, because of the actual irradiation of live pigs a DIRQA had to be made, to ensure the validity of DIR. Description of the procedure will be given here, alongside with the results.

Materials and Methods

Pig irradiation experiment

DIR and DIRQA procedures will be given here, while a detailed description of the whole pig irradiation experiment can be found elsewhere [Lehmann et al., 2015a]. Cardiac gated contrast-enhanced CT scans (4D-CT-cardiac) were made on 15 pigs with a multidetector 64 row Siemens Somatom Definition Flash scanner (Siemens Healthcare, Forchheim, Germany) with 1 mm voxel and 1 mm slice spacing. There was no breathing motion present, since a breath-hold technique was used. Cardiac motion was based on electrocardiography (ECG) and was divided into 10 sequential phases (0-9). 8 pigs had a pacemaker implemented, because the irradiation was planned to disturb the heart rhythm and a pacemaker should compensate for that. Pigs are therefore divided into two groups, with pacemaker (PM), $n = 8$, and without one (noPM), $n = 7$.

After CT acquisition, DIR on 4D-CT-cardiac was made using B-Spline Plastimatch module in Slicer (see Section 2.2.2). Details on parameters used for DIR can be found in Table 2.3. Phase 0 was chosen as a reference phase. Phase 3 corresponds to a maximum heart contraction with likely the biggest motion. All other phases were registered to reference phase with inverse registration as well. A checklist was made to follow DIR and DIRQA for quality assurance. An example of a filled-out checklist is shown in Fig. 2.12a.

Based on lung patient DIR and because of the time constraints in the study workflow, DIRQA was made only on DIR from phase 5. DIRQA consisted of default and true absolute difference, true Jacobian and ICE. DIRQA results were stored in a text file (example shown in Fig. 2.12b) and users checked if the values did not exceed expected ones: Mean absolute difference should be smaller than 1; mean Jacobian should be 1; mean ICE should be smaller than 2 mm. ROI was manually created in Slicer to encompass the pig body and then used in all DIRQA checks.

After a successful DIR and DIRQA vector fields were used in a treatment planning and the resulting plans were used in the pig irradiation experiment.

Around 20 minutes were needed for each pig DIR and additional 20 minutes for pig DIRQA. Calculations were done on a Linux computer with 8 CPU cores and 32 GB RAM.

Table 2.3: Parameters used for Plastimatch registration. A mean squared error metric was used. Details for each parameter can be found here [Plastimatch, 2016].

Parameter	Stage 1	Stage 2
Resolution	4,4,2	2,2,1
Grid size	50	15
Regularization lambda	0.005	0.005
Iterations	200	100

Post-experiment analysis

After the conclusion of the animal study, a more detailed DIRQA was made, with all motion phases included in DIRQA. In addition to original checks explained in previous section, vector field magnitudes were analyzed, inverse absolute difference and Jacobian were calculated. Paired t-tests were used to test statistical significance for vector field magnitudes between true and inverse vector fields and PM and noPM groups.

(a)

Checkliste Bestrahlungsplanung

DOSE: 40 Gy TARGET: PV SCHWEIN: Uniform

Scripts path: AIXd/user/motion/Beamtime/GSI1407/Simulations/SCRIPTS

Heartbeats during CT: N: 45 bpm Final motion: Sin_3mm_1200ms0

Task	Script	Done?	Name	Date
Create Header		✓	AE	17.07.
Copy CT data to PatientData2		✓	AE	17.07.
Sort CTs (contrast/native)		✓	AE	"
Sort motion phased		✓	AE	"
Check # of files in each phase	CTX.sh	✓	AE	"
Check contrast and native slices	"	✓	AE	"
Create CTX	"	✓	AE	"
Create MHA	"	✓	AE	"
Check BB coordinates and write Header		✓	AE	"
Copy Contours		✓	AE	18.07.
Create VDX		✓	AE	"
Change 0 to 1 for Target (VDX)		✓	AE	"
Check voi names in VDX		✓	AE	"
FalseColorCheck contrast<->native (00)		✓	AE	17.07.
Contours native ok?				
Registration contrast -> 4DCT		✓	AE	17.07.
Registration ok?		✓	AE	17.07.

(b)

DIRQA for: Registration Node Contrast 4D

InvVector

x: 4.01

y: 3.59

z: 4.1

Vector

x: 4.53

y: 4.11

z: 4.49

RelativeAbsoluteDifference

Mean: 0.81

STD: 0.59

Jacobian

Mean: 1.0

STD: 0.05

Max: 1.48

Min: 0.65

InverseConsistency

Mean: 0.11

STD: 0.17

Max: 1.97

Min: 0.0

Figure 2.12: (a) Part of the checklist for quality assurance during pig irradiation. DIR and DIRQA part is highlighted in red and consisted of two steps. First DIR was made on 4D-CT-cardiac and afterwards DIRQA was made on DIR from phase 50%. End result was presented as text shown in (b). Relative absolute difference stands for ratio between true and default absolute difference.

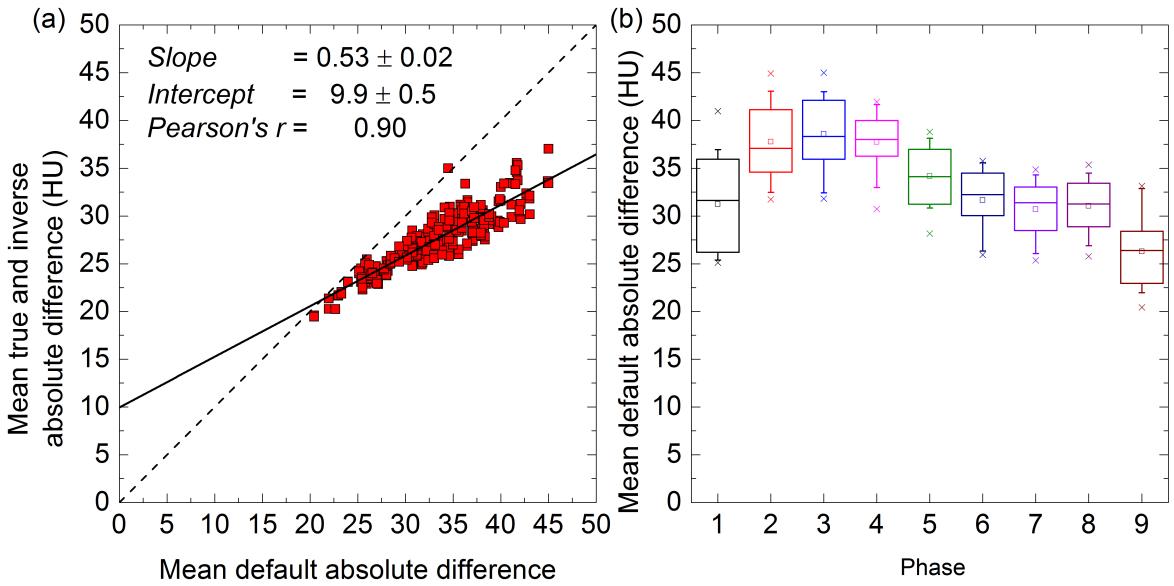


Figure 2.13: (a) Mean true and inverse absolute difference plotted against mean default absolute difference. Solid line shows linear fit, with parameters written in corner. Dashed line shows $y(x) = x$. (b) Box plots of mean default absolute difference distribution across nine 4D-CT phases. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

Results

An example of pig DIR is shown in Fig. 2.14. One DIRQA during animal study showed higher mean true absolute difference than mean default absolute difference. The registration was therefore repeated with three stages instead of 2. Third stage had 100 iterations with resolution size “1, 1, 1“ and grid size ”10“. All other DIRQA checks were positive.

Post-experiment statistical analysis on vector field magnitudes is shown in Table 2.4. No statistical difference was observed between true and inverse vector fields. However, significant difference was observed between vector field magnitudes of PM and noPM groups. Contributions to vector field magnitudes from three axis were equal.

Table 2.4: Data for vector magnitudes. Values are presented as mean (range).

	PM		noPM	
	True vector field	Inverse vector field	True vector field	Inverse vector field
Mean	0.08 (0.03 - 0.16)	0.08 (0.03 - 0.14)	0.07 (0.0 - 0.18)	0.06 (0.0 - 0.17)
STD	0.4 (0.09 - 0.78)	0.36 (0.08 - 0.68)	0.3 (0.05 - 0.77)	0.28 (0.04 - 0.71)
Max	8.24 (1.6 - 17.33)	7.98 (0.7 - 17.76)	5.9 (0.97 - 15.91)	5.38 (1.08 - 12.42)

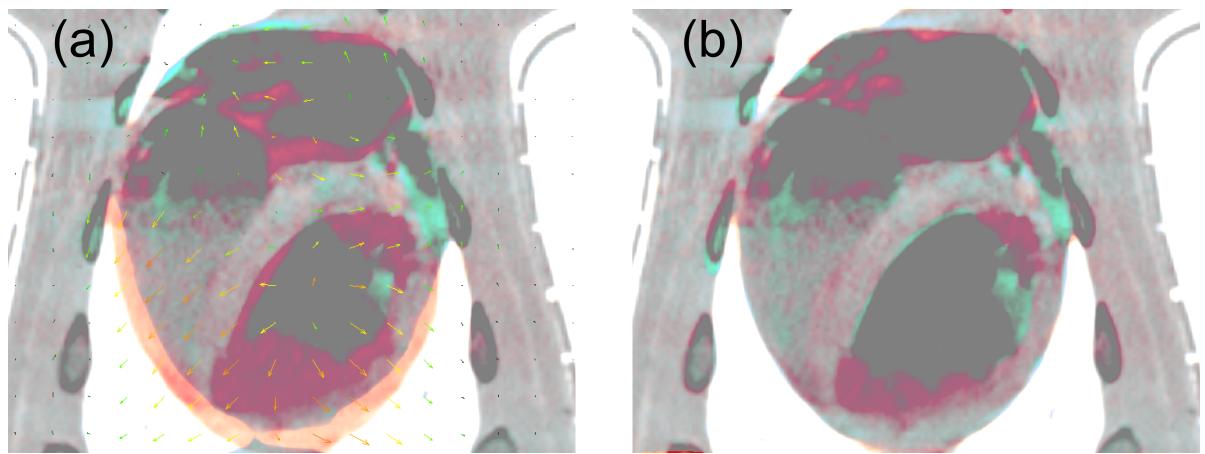


Figure 2.14: Inverse color overlay of two phases before (a) and after (b) DIR. Vector field is displayed on image (a) as arrows.

Dependence of true and inverse absolute difference on default absolute difference with a linear fit is shown in Fig. 2.13a. Default absolute difference distribution across 9 phases can be seen in Fig. 2.13b.

Distribution of Jacobian and ICE results are shown in Fig. 2.15. Maximum values of true and inverse Jacobian and maximum ICE were tested against maximum vector magnitudes and fitted with linear function. Results are plotted in Fig. 2.16.

All linear fits in Fig. 2.13 and 2.16 were statistically significant ($p < 0.05$).

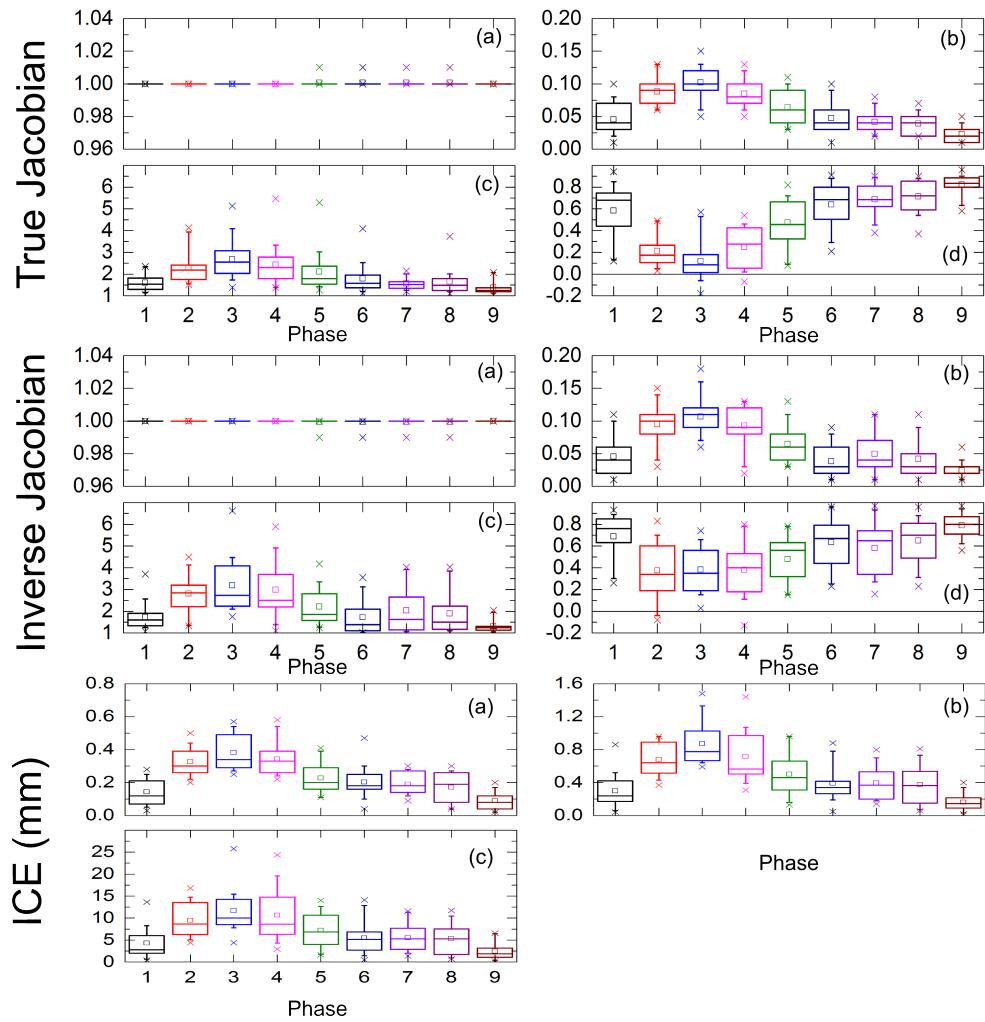


Figure 2.15: Statistical data for true (top) and inverse (middle) Jacobian and ICE (bottom) for 9 4D-CT-cardiac phases (reference phase 0 is excluded) for 15 pigs. Mean, STD, maximum and minimum are represented as (a), (b), (c) and (d), respectively. Minimum ICE is 0 throughout all phases and pigs. Boxes represent 25-75%, whiskers 10-90% of data, median is shown with solid line, mean with square and outliers with crosses.

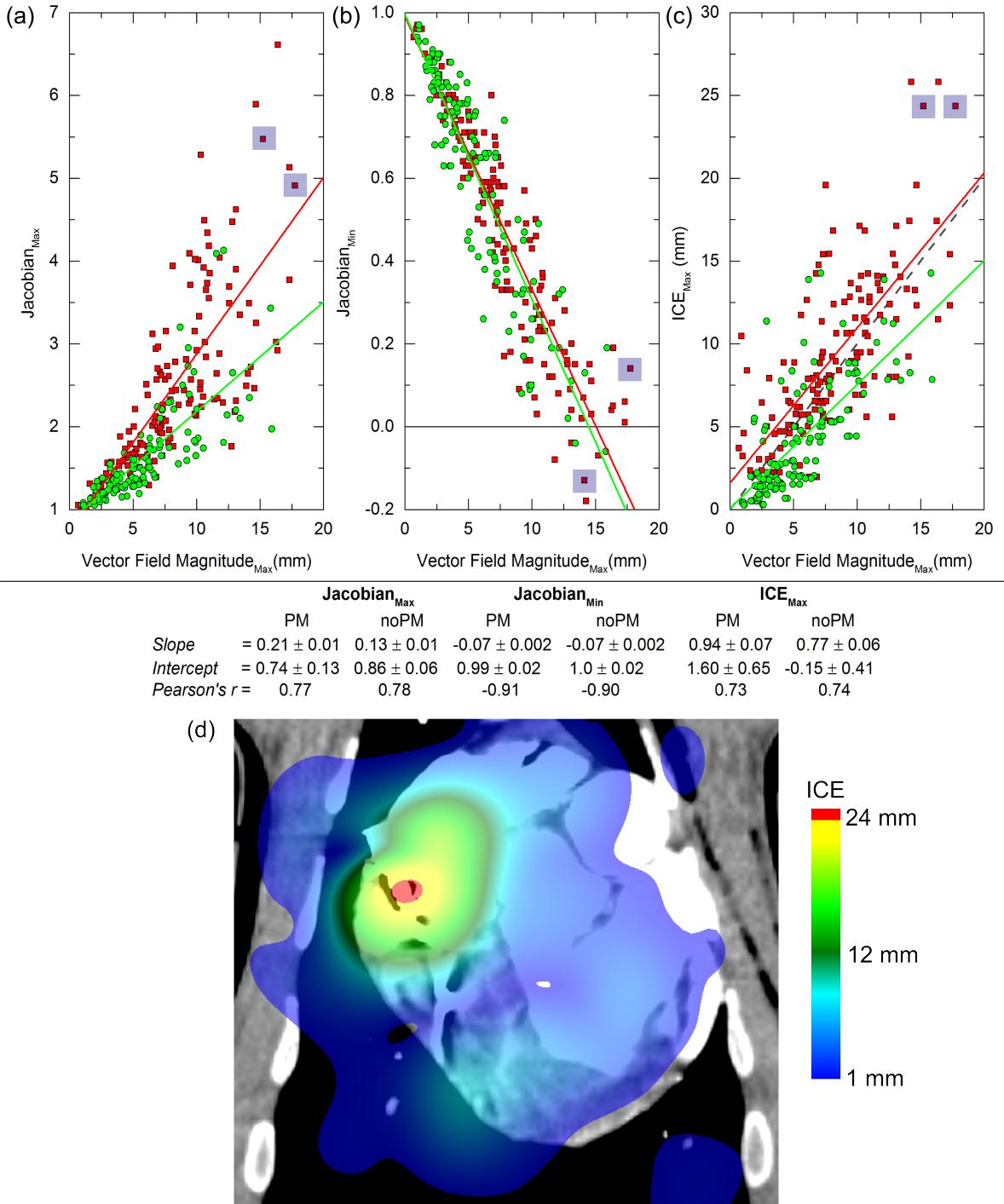


Figure 2.16: Values of maximum Jacobian (a), minimum Jacobian (b) and maximum ICE (c) plotted against maximum vector magnitudes. Linear fit is displayed with solid line and its parameters are written below the plots. Dashed line in (c) shows $y(x) = x$ plot. Values from pig on image (d) are highlighted with blue squares in (a)-(c). PM and noPM are shown with red squares and green circles, respectively. ICE is displayed on (d) using color table as displayed in legend.

Discussion

All 15 pig 4D-CTs have been registered, which resulted in 270 DIR. DIRQA was done in two steps - a smaller DIRQA during animal study and a complete DIRQA after it.

Mean vector field magnitudes were small (approx. 0.1 mm), since pigs were in a breath-hold position and the only motion was the beating of the heart. Despite the small mean vector magnitude it was still enough to observe statistical difference between the PM and noPM. Consequently, the difference between the two groups is consistent throughout the DIRQA.

The DIR did well in terms of lowering the absolute difference metric. There was a strong correlation between default versus true and inverse absolute difference. The slope from linear fit on Fig. 2.13 has the same value than the slope from lung 4D-CT (see Fig. 2.8), showing the effectiveness of B-Spline algorithm. The distribution of default absolute difference across different phases is smaller than in lung 4D-CT (10 HU compared to 35 HU), due to the fact there was less motion present in a pig 4D-CT. The shape of default absolute difference distribution persist then in the Jacobian and ICE distributions as well.

A good result in absolute difference does not necessarily mean a good DIR, as can be seen from Jacobian and ICE checks. The mean Jacobian and ICE were 1 and 0, respectively, since the vector fields were small on average. However there were large deviations present in Jacobian and ICE. Most notably, there were a few cases of negative minimum Jacobian which would suggest organ folding. Since organ folding did not occur during a heart beat, negative minimum Jacobian points to inconsistencies in DIR.

The large deviations in Jacobian and ICE can in part be explained with large maximum vector field values, as shown in Fig. 2.16. All linear fits have a good correlation, with no difference between PM and noPM in the quality of the fits. The actual linear fit parameters, however, further show the inconsistencies in DIR. The clearest example of inconsistencies in DIR is with linear fit from maximum ICE PM, which lies above $y(x) = x$ function. This means that there were points further away from starting point after true and inverse transformation, then just after true transformation. The linear fit for noPM maximum ICE showed better results in this terms, since it lied below $y(x) = x$ function.

During animal study only one DIR was repeated because of DIRQA. It was shown in post-experiment analysis, that all DIR should be repeated, pointing out flaws in initial DIRQA procedure. Mainly, DIRQA should be made on all DIR and not just on one phase, since DIRQA from one DIR does not guarantee the quality of the other DIRs from the same 4D-CT. Each DIR is performed individually and should be treated as such. Furthermore, instead of mean Jacobian and ICE, maximum and minimum should be investigated, because it points to the worst part of the DIR.

2.4 Summary and Discussion

Tools to perform DIR and DIRQA were presented in this chapter. Different modules were written for an open-source software Slicer that can handle large DIR problems, such as registering whole 4D-CTs. In addition to DIR, the modules can also calculate DIRQA on DIR warped images and vector fields with several different checks. The main objective of this work was to provide systematic approach to DIR and to give parameters on DIRQA that can estimate the quality of DIR. A first analysis of DIRQA checks was done on a large DIR database - 684s DIR were checked in total.

Most of the work was based on Slicer, which is well-established software in medical research. To date, there are more than 500 publications that have used Slicer in their research [Slicer, 2016b], with topic ranging from teaching [Pujol et al., 2016], disease staging [Liu et al., 2015, Liu et al., 2016a], motion tracking [Behringer et al., 2015] to image reconstruction [Meyer et al., 2015], image registration [Li et al., 2015b, Fedorov et al., 2015, Li et al., 2015a] and others. Slicer offers different functionalities and is especially suited for research, since it can be modified to specific needs. However, it is important to stress that Slicer is not a medical application. Additionally, Slicer can sometimes be unstable with unexpected crashes. It is constantly under development and more and more errors are fixed with each new release. New releases also bring new functionalities, but there can be problems with back-track compatibility. Even though there are some disadvantages to using Slicer, its advantages outweigh them and make Slicer a useful tool, as was shown in this chapter.

Results shown in this chapter were obtained with B-Spline DIR algorithm. Several other algorithms exist, demons most commonly used alongside B-Spline [Thirion, 1998]. Varadhan et al. compared B-Spline and demons DIR for lung case [Varadhan et al., 2013] and showed that B-Spline is superior to demons, especially if there is difference in contrast between images. They used a mutual information metric, to account for differences in contrast. Images used in this chapter were either all without (lung 4D-CTs) or all with (animal study 4D-CTs) contrast agent, therefore there was no difference in contrast between images and mutual metric could not be used.

A designated module was made for DIRQA. The main advantage of the DIRQA module is that all different techniques are gathered in a single place and can be used on a specific case. The ease of use is also essential, for DIRQA to find its way into clinical work flow. A test of using DIRQA in potential clinical work flow was done at GSI during the animal study, where different users had to use both DIR and DIRQA modules. The experiment was also under time pressure, since there was a scheduled beam time. 4D-CTs were acquired approximately two weeks before scheduled irradiation. During this two weeks contour delineation, DIR, DIRQA, treatment planning and treatment planning QA had to be done [Lehmann et al., 2015a]. There were already

propositions for frameworks for DIRQA in clinical work flow [Varadhan et al., 2013], however none were tested in an actual clinical environment.

The techniques used in DIRQA can be divided into visual qualitative (inverse color, checkerboard) and quantitative (absolute difference, Jacobian and ICE). While the quantitative can be used to pinpoint errors in DIR, the visual qualitative can be used to actually locate the error as shown in Fig. 2.10d. The location and size of DIR error also determines if a repetition of DIR is necessary. All three quantitative checks have been used in literature as a possible DIRQA [Varadhan et al., 2013, Leow et al., 2007, Christensen and Johnson, 2001, Bender and Tomé, 2009]. They all share the same flaw, however, that they are a necessary but not sufficient condition for a successful DIR. One common DIRQA check in literature that our module is currently missing, is comparison of anatomical correspondence - comparison between reference, moving and warped contours. Ideally warped and reference contour should be the same. Two metrics are usually used in contour comparison - dice similarity coefficient [Varadhan et al., 2013] and Hausdorff distance [Huttenlocher et al., 1993]. Slicer already has functionalities for both contour comparison checks, so they could be used. The biggest disadvantage of anatomical correspondence check is that contour delineation is required in both, reference and moving phase, which is scarcely done by physicians, since it takes too much time. Additionally, the anatomical correspondence check does not judge the vector field quality inside contour. Lack of contours in both reference and moving phase was the reason the anatomical correspondence check was not used.

Studies on DIRQA so far have focused on a small number of DIR cases, whether it is phantom [Mutic et al., 2001, Moore et al., 2004] or patient studies [Wu et al., 2008, Varadhan et al., 2013]. With a small number of DIRs, it is possible to thoroughly examine each DIR and hence understand DIRQA. In this chapter a different approach was used. Rather than examining each DIR individually, a large dataset was analyzed and common traits for DIR were found. Due to differences in anatomical sites, DIRQA parameters have to be found for each anatomical site individually, since they can deviate significantly, as seen by two different cases presented here. However, three checks are independent on anatomical site: mean true and inverse consistency should be higher than default absolute difference, Jacobian should be positive and ICE should be smaller than maximum vector field magnitudes. If any of these checks fails, DIR needs to be investigated and, if necessary, repeated.

DIR of lung 4D-CT can be considered relatively easy, since the changes between phases are small and the contrast between lungs and other tissue is high. This is confirmed by the mean value of Jacobian 1 and mean ICE smaller than 1 mm. The maximum and minimum Jacobian and ICE are more interesting, since they show DIR inconsistencies. All ICE values bigger than maximum vector field magnitudes were found to originate from areas with poor DIR. An effect of poor DIR can be seen in Fig. 2.11, where propagated liver and lung contour do not match features on the image. An image artifact was the reason for the poor DIR. After investigation

of poor DIR location and size, it was decided, that DIR does not require repetition, due to large distance between poor DIR and the tumor.

If the DIR of lung 4D-CT was considered relatively easy, opposite holds true for DIR of animal study 4D-CT. The motion of the heart during a heartbeat is complex, with muscles stretching and contracting in different directions [Seeley et al., 2007]. Furthermore, the volume of blood shifts from one ventricle to the other. In the case of 4D-CT-cardiac blood carried a contrast agent, therefore different phases in 4D-CT-cardiac had different distribution of HU in different parts of the heart. Additionally, it is well established that pacemakers cause several complications in a CT scan [Mak and Truong, 2012]. This was confirmed by the differences observed between PM and noPM. Clearest example is the PM linear fit of maximum ICE in Fig. 2.16, which is above $y(x) = x$. For noPM the linear fit is below $y(x) = x$, however the slope has still a value of 0.77, compared to 0.38 of a lung 4D-CT fit. Inconsistencies in DIR were further supported by negative minimum Jacobian, which were found for both, PM and noPM groups. Negative minimum Jacobian and large ICE values are clear indicators, that DIR in heart can not be accepted for heart treatment planning and needs to be repeated. An effect of DIR on actual irradiation also has to be examined. The DIR of cardiac 4D-CT is currently under careful investigation and several different solutions, such as artifact removal and different registration parameters are being tested.

In the future, the DIRQA module should undergo further testing. In addition to checking DIRQA on different anatomical sites and between different modalities, it should be investigated how good is DIRQA at spotting inconsistencies in DIR, i.e. what is the number of false negatives. Furthermore, with more data analyzed, the parameters in DIRQA checks should get more precise, so outliers could be easier spotted.

3 Comparison of Photons versus Carbon Ions in Single Fraction Therapy of Lung Cancer

3.1 Introduction

Lung cancer is one of the leading medical problems worldwide with approximately 1.4 million deaths per year [Siegel et al., 2014]. Surgery is usually the first choice in treating localized non-small cell lung cancer (NSCLC). However, in recent years stereotactic body-radiation therapy with photons (SBRT) showed very promising results, with high local control-rates of NSCLC [Baumann et al., 2009, Fakiris et al., 2009, Grutters et al., 2010, Ricardi et al., 2010, Timmerman et al., 2010, Greco et al., 2011].

Scanned particle therapy can produce sharp dose gradients with a finite range of the beam and can thus provide higher healthy tissue sparing. This reduces both side effects as well as the risk of secondary cancer [Newhauser and Durante, 2011]. Treatment of lung tumors with particles is still challenging due to interplay and radiological path length changes [Bert and Durante, 2011]. The latter can be substantial when dense tissue (e.g. the solid tumor mass) is replaced with low-density tissue (lung) due to motion.

Grutters et al. have performed a meta-analysis on comparison between photon, proton and carbon ions in treating NSCLC [Grutters et al., 2010]. They found similar 5-year survival rates for SBRT, protons and carbon-ions (around 40%). However, the number of patients treated with particle therapy was low and they advise caution when interpreting the data. Also different fractionation schemes were used in the comparison. A more recent review was published by Kamada et al. [Kamada et al., 2016] where they reported a high 3-year survival rate for single-fraction carbon-ions (76.9%), with no late treatment-related adverse effects. In comparison, SBRT had 55.8% 3-year survival rate, with 10 - 27% of patients exhibiting grade 3 treatment-related adverse effects [Timmerman et al., 2010]. It is important to note that all of these studies used passive beam scattering, avoiding the problem of interplay between organ motion and scanning beam motion. On the other hand, active beam scanning can provide even better dose shaping which becomes essential in high dose single fractionation regimes. The effects of motion and motion mitigation techniques on scanned carbon ion dose distribution therefore need to be considered in a fair comparison of photons and carbon ions.

To evaluate potential advantages of active scanning with carbon ions (PT), an in silico comparison of simulated PT plans to SBRT plans actually delivered was conducted. Target coverage and a wide range of OAR doses were assessed both with and without simulated motion on time-resolved computed tomographies (4D-CTs).

3.2 Materials and methods

3.2.1 Patient data

The study included 19 patients with in total 26 lesions that were actually treated with SBRT at the Champalimaud Centre for the Unknown, Lisbon (Portugal). The lesion size was 2.9 cm³ (median, 25-75% 1.4 - 9.7) and peak-to-peak motion was 3.1 mm (1.6 - 5.6). Three patients had two targets, one had five and the rest one. 13 lesions were right-sided, 12 were left-sided and one was located in right cardiophrenic space. An overview of tumor characteristics can be found in Table 3.1. Two CTs were available for all patients. A planning CT was used for OAR delineation and SBRT planning. Target motion was estimated on a 4D-CT, consisting of 10 phases (0% - 90%). Clinical target volumes (CTV) were delineated using a registered positron emission tomography (PET) scan.

The planning objectives were that 99% of planning target volume (PTV) must receive at least 24 Gy ($D_{99\%} \geq 24$ Gy) in a single fraction, while all OAR constraints as defined in the AAPM task group 101 report on stereotactic radiotherapy had to be respected [Benedict et al., 2010].

Table 3.1: Lesion characteristics, with lesion locations, stages, peak-to-peak motions and volumes of corresponding CTV, PTV_{SBRT} and PTV_{PT} . Abbreviations for lesion location are: RSL, right superior lung; IRL, inferior right lung; LSL, left superior lung; ILL, inferior left lung; RCS, right cardiophrenic space.

Number	Location	Stage	Peak-to-peak motion [mm]	Volume (cm^3)		
				CTV	PTV_{SBRT}	PTV_{PT}
1	LSL	IIa	4.8	35.9	100	179
2	LSL	Ia	3.1	1.6	7.7	40.6
3	IRL	IV	12	2.3	11.6	32
4	RSL	Ia	0.5	6.9	25.2	38
5	ILL	IV	4.4	2.5	15	20.5
6	ILL	IV	7.5	1.4	7.7	26.5
7	RSL	IV	3.9	16	40	72.5
8	ILL	IV	0.6	139	261	255
9	LSL	IV	2	9.2	35	46.5
10	IRL	IV	3.4	10.2	38	45.5
11	ILL	IV	2.8	14.4	46.4	57.2
12	ILL	IV	5.8	3.8	17.4	23.4
13	RSL	IV	0.8	4.3	17.7	26.3
14	LSL	IV	3.4	2.7	14.5	23.1
15	RSL	IV	2.1	3.1	15.4	33.5
16	LSL	IV	0.5	0.5	5.4	6.7
17	ILL	IV	7.8	0.8	6.1	23.5
18	LSL	IV	0.1	1.7	15	23.5
19	IRL	IIIb	11.4	27	137	118.5
20	RSL	Ia	2.2	1.7	10	23.4
21	RSL	IV	0.2	0.9	3.2	14.9
22	RSL	IV	2.2	3.9	22.1	27.5
23	LSL	IV	3.1	9.8	28	51
24	RSL	IV	8.1	0.6	3.3	4.1
25	LSL	IV	1.4	0.8	5.9	10
26	RCS	IV	11.8	0.4	6.6	8.6

3.2.2 Planning target volume definition

To account for range changes relevant for particles only, different PTV definitions were used for SBRT and PT, as shown in Fig. 3.1. Within this chapter they will be named PTV_{SBRT} and PTV_{PT} for SBRT and PT, respectively. In SBRT, the responsible clinician determined the maximum breathing motion of the CTV from the 4D-CT, hence creating an ITV. This ITV plus an additional 3 mm for setup uncertainty yielded the PTV_{SBRT} .

PTV_{PT} was constructed following principles from Graeff et al [Graeff et al., 2012]. Each beam has a unique PTV_{PT} . For setup uncertainty margins of 3 mm laterally and 1 mm in beam's eyes

view (BEV) were used on the CTV. Afterwards a water-equivalent path length ITV (WEPL-ITV) was build, using transformation maps from the B-Spline deformable registration of the 4D-CT data [Shackleford et al., 2010]. Additional 2 mm + 2% proximal and distal margins were added in BEV to account for uncertainty from Hounsfield units to water equivalent path length conversion. If the target overlapped with an OAR (e.g. small airways) then OAR plus a margin of 2-5 mm was subtracted from PTV_{SBRT} or PTV_{PT} .

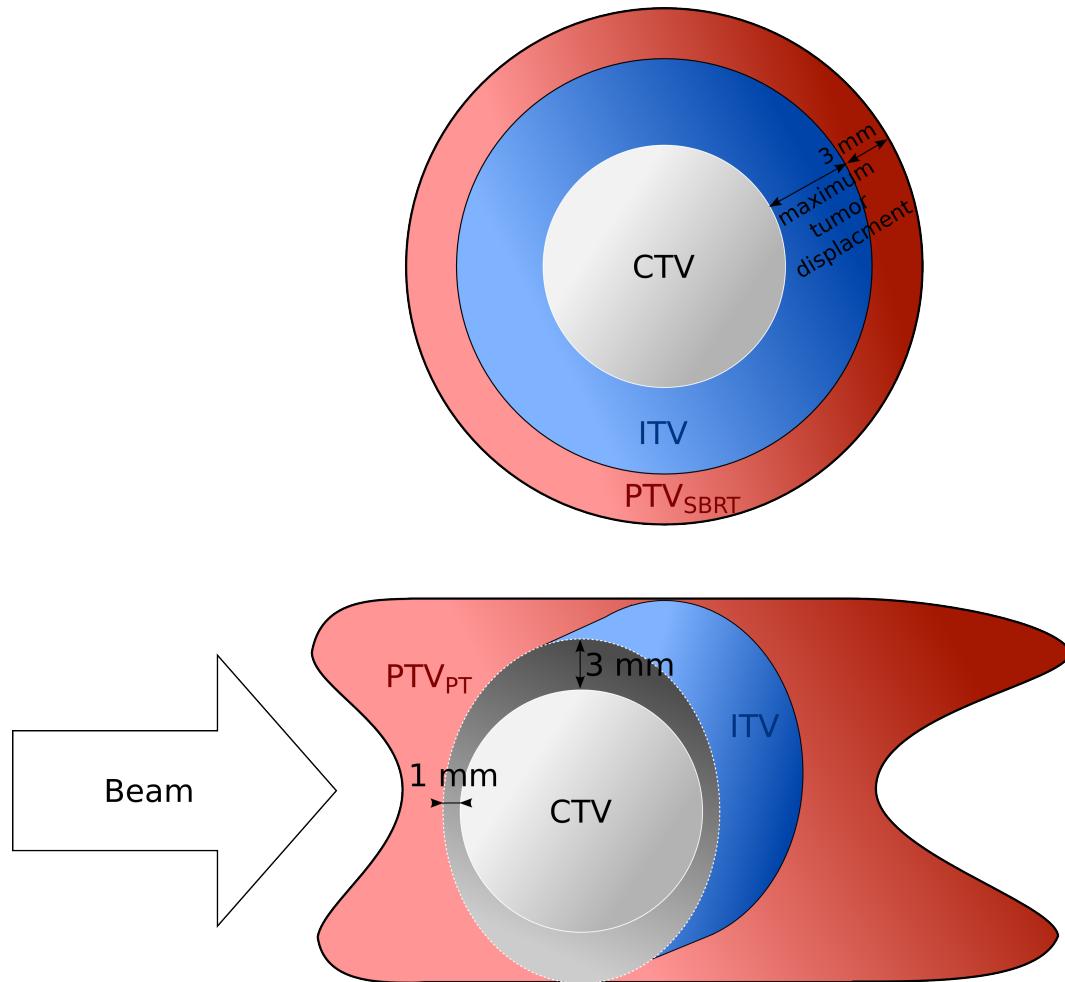


Figure 3.1: Different PTV definitions for SDRT (PTV_{SBRT}) and CiT (PTV_{PT}). For PTV_{SBRT} isotropic margins of 3 mm plus maximum tumor displacement due to breathing were used on the CTV; For PTV_{PT} margins of 3 mm laterally and 1 mm in beam's eye view were used and then range-ITV was constructed with 2 mm + 2% range margins added for PTV_{PT} in end-inhale phase.

3.2.3 SDRT treatment planning

The clinical plans were calculated with the Eclipse v10 planning system (Varian Medical Systems, Palo Alto, USA) using the AAA beam model. They were all VMAT plans generally consisting of 4 overlapping partial arcs, 2 in clockwise and 2 anticlockwise direction, with a gantry range of typically 200°. For tumor sizes > 2.5 cm a calculation grid of 2.5 mm was used, otherwise this was 1 mm. During optimization, a first iteration included the PTV_{SBRT} only, after which the OARs were added. In order to lower OAR dose and improve the PTV_{SBRT} homogeneity, we created an artificial shell of 2 cm around the PTV_{SBRT} and minimized the dose there as well. During optimization the fast Multi Resolution Dose Calculation (MRDC) model was used, with one intermediate step using the slower but more accurate AAA model to get an adequate PTV_{SBRT} coverage after optimization.

3.2.4 Carbon-ions treatment planning

For PT, state of the art 4D treatment planning software TRiP98 was used [Richter et al., 2013]. A single field uniform dose plan (SFUD) was optimized on the PTV_{PT} in the end-inhale reference phase of the 4D-CT. Most targets ($n = 20$) were planned with two fields. For the remaining targets, one ($n = 1$), three ($n = 3$) or four ($n = 2$) fields were used due to proximity of OARs. A regular grid of beam spots with a spacing of 2 mm, a beam spot full width at half maximum (FWHM) size of approximately 6 mm and a 3 mm ripple filter were used. To compensate for short particle ranges in lung tissue, a bolus of 80 mm water-equivalent thickness was added.

The relative biological effectiveness (RBE) following the local effect model (LEM) IV [Elsaesser et al., 2010]. For a conservative estimation, an alpha-beta ratio of 6 Gy and 2 Gy were used for target and OARs, respectively. This led to an RBE of approximately 1.1 in target tissue and approximately 1.1 to 3 in OARs. Dose was calculated on end-inhale (3D-Dose_{0%}) and end-exhale (3D-Dose_{50%}) phases. 4D dose delivery was simulated as described by Richter et al [Richter et al., 2014]. Two different breathing periods (3.6 and 5 s) and two different starting phases (0° and 90°) were used. Simulations without motion compensation (4D-Dose_{interplay}) and with slice-by-slice raster rescanning were performed (4D-Dose_{rescan}). Five rescans were used for the majority of targets ($n=24$), whereas 20 rescans were used for targets where the interplay effects were too big to achieve a satisfactory target coverage ($n = 2$; lesions 3 and 18 in Table 3.1).

3.2.5 Dose metrics and analysis

For comparison between SBRT and PT the following dose metrics were used - for the target the minimum dose in 99% of the volume ($D_{99\%}$), which should be higher than 24 Gy; for OARs, the

maximum point dose (D_{Max}) and the mean dose (D_{Mean}). Additionally, the volume receiving 20% of the planned dose ($V_{20\%}$) was used to assess differences in lung doses. In all cases, absorbed dose in Gy for SBRT was compared to biologically-equivalent dose in Gy(RBE) for PT.

Paired t-tests were performed to compare the dose metrics and for post-hoc exploratory analysis between groups a two-sided t-test with Welch correction for different variances was carried out. A p-value < 0.05 was considered significant. Dose differences are always reported such that higher dose levels for SBRT result in positive values.

3.3 Results

Examples of two SBRT and 4D-Dose_{rescan} PT treatment plans are shown in Fig. 3.2. Patient 9 has two lesions in close proximity to the spinal cord. Patient 2 has a small lesion (1.6 cm^3) in the superior position of the left lung. $D_{99\%}$ is 100% for SBRT and PT in all CTVs for Patient A and B; average OAR difference between SBRT and PT in D_{Max} is 5.1 Gy and 1.4 Gy and in mean dose 1.4 Gy and 0.7 Gy, respectively for patient A and B.

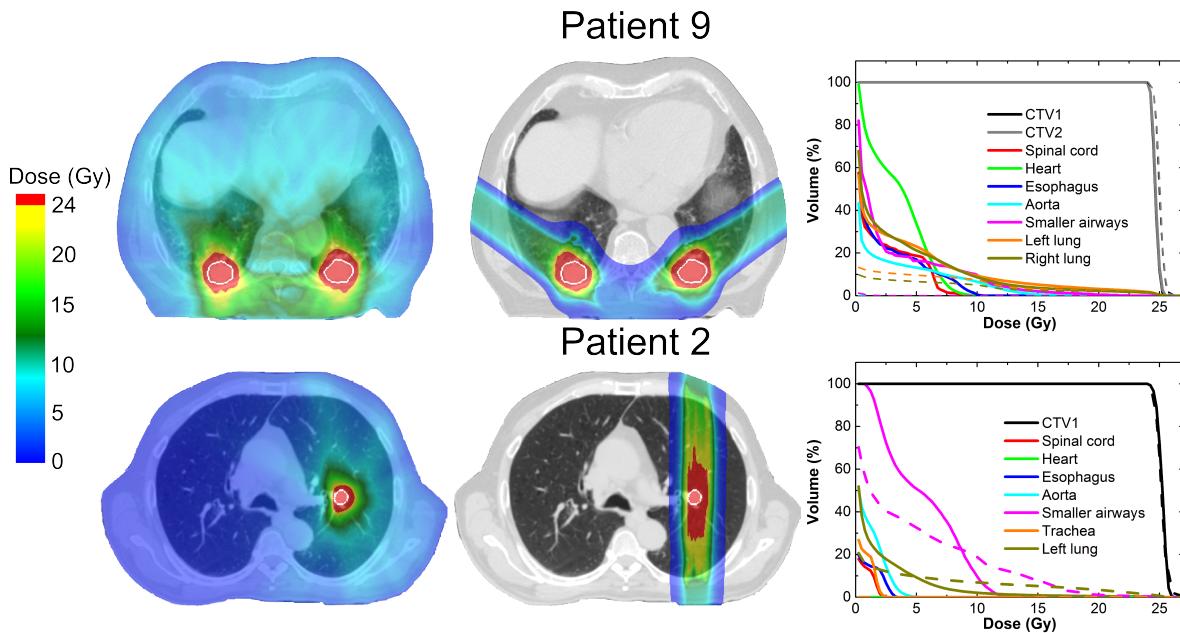


Figure 3.2: Treatment plans for SBRT (left), PT (middle) and dose volume histogram (right) for SBRT (solid lines) and PT (dashed lines) for two patients. PT curves for OARs without any dose are not shown. Patient 9 (top row) might be better suited for PT and patient 2 (lower row) for SBRT. Patient 2 has a small lesion (1.6 cm^3) in a central lung region, resulting in large PTV_{PT} - up to 32 cm^3 , compared to PTV_{SBRT} 7.7 cm^3 . The CTV contour is outlined in white.

3.3.1 Target Coverage

Difference in PTV definition resulted in 1.5 (1.3 - 2.1) times bigger PTV_{PT} than PTV_{SBRT} . All SBRT plans were clinically acceptable, though in one case the $D_{99\%}$ was reduced to 16.8 Gy due to proximity of an OAR. 3D-Dose_{0%} and 3D-Dose_{50%} plans provided sufficient target coverage in all patients. For 4D-Dose_{interplay} and 4D-Dose_{rescan} there was 63% and 2% cases of insufficient target coverage, respectively, across all targets and different breathing patterns. Details are shown in Fig. 3.3. For the patient with reduced dose in SBRT, PT could increase the $D_{99\%}$ from 16.8 Gy in SBRT to 20.3 Gy while adhering to OAR constraints.

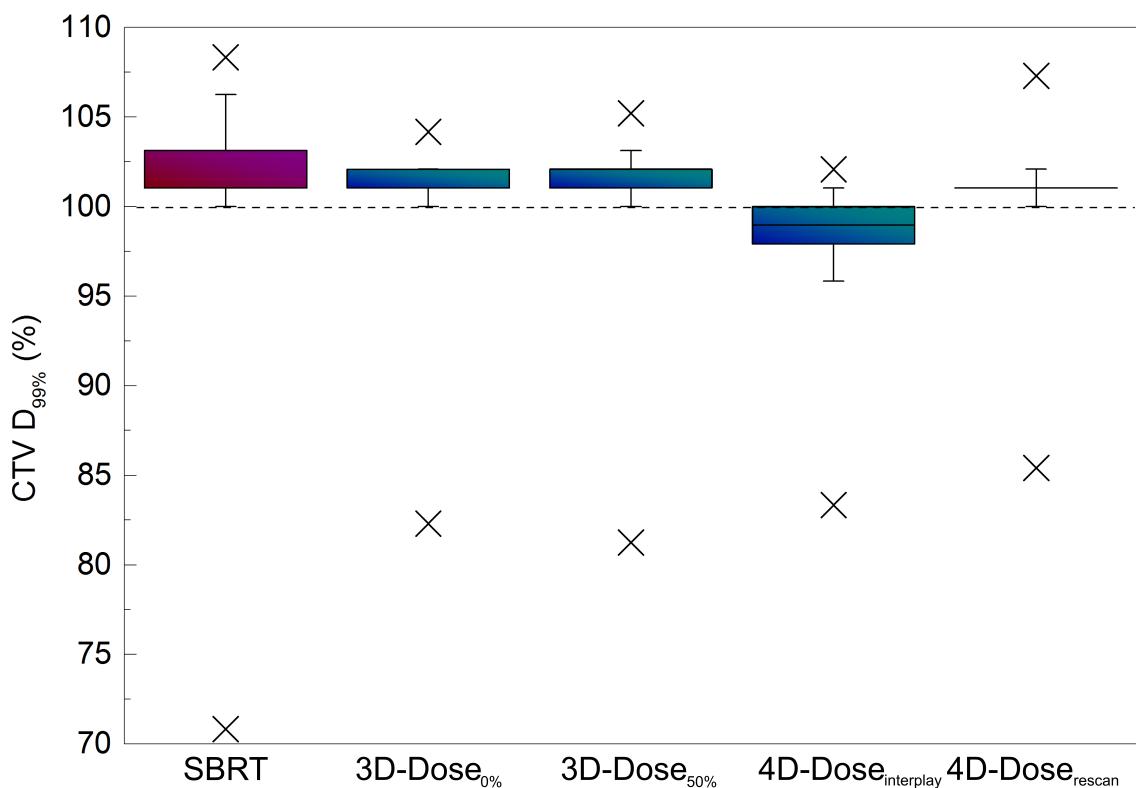


Figure 3.3: CTV $D_{99\%}$ for SBRT and different PT calculations. Four different breathing patterns are included for all targets in 4D-interplay and 4D-rescan. The dashed line shows the lower limit for clinical acceptance. One patient was an exception where lower target dose was accepted due to the proximity of a critical structure.

3.3.2 Dose in OARs

There was no significant difference in dose to OAR between the different PT dose calculations. The D_{Max} and D_{Mean} for SBRT and 4D-Dose_{rescan} for OARs heart, spinal cord, smaller airway esophagus, trachea, aorta, ipsi- and contralateral lung are presented in Table 3.2. There was a significant difference in both D_{Max} and D_{Mean} for all OARs between SBRT and PT, with PT delivering less dose to OARs. Significant difference was also observed for $V_{20\%}$ for ipsilateral lung, which was 15.3% (9.6 - 23.5) and 10.3% (7.9 - 13.7) for SBRT and PT, respectively. The $V_{20\%}$ for contralateral lung was zero for almost all patients in SBRT and PT. The overall OAR difference for patients between SBRT and PT was significant, 2.8 Gy (1.6 - 3.7) for D_{Max} and 0.7 Gy (0.3 - 1.6) for D_{Mean} .

Table 3.2: Dose metrics for OARs. First value at each organ is from SDRT and the second from 4D-rescan. All values are shown as median and 25-75% in brackets.

OAR	D_{Max} (Gy)		D_{Mean} (Gy)	
	Photon	Carbon	Photon	Carbon
Heart	6.0 (0.3 - 11.6)	0 (0 - 8.8)	1.3 (0.1 - 2.2)	0 (0 - 0.5)
Spinal Cord	5.5 (3.3 - 8.5)	0 (0 - 0.5)	0.7 (0.3 - 1.2)	0 (0 - 0)
Smaller Airways	13.0 (9.8 - 17.1)	10.3 (3.3 - 19.1)	2.8 (1.5 - 5.8)	0.5 (0 - 2.6)
Esophagus	5.8 (3.9 - 8.4)	0 (0 - 0.3)	1.1 (0.6 - 1.5)	0 (0 - 0)
Trachea	3.9 (1.8 - 5.4)	0 (0 - 0)	1 (0.3 - 1.3)	0 (0 - 0)
Aorta	8.0 (5.1 - 21.9)	3.9 (0 - 18.1)	1.4 (0.7 - 1.6)	0.1 (0 - 0.4)
Ipsilateral Lung	26.3 (26.0 - 26.5)	26.3 (25.8 - 26.5)	1.9 (1.5 - 3.0)	1.9 (1.4 - 2.5)
Contralateral Lung	5.0 (3.5 - 9.6)	0 (0 - 0.9)	0.4 (0.2 - 0.6)	0 (0 - 0)

3.3.3 Dependence on CTV Size

Significant differences were observed between patients with a single CTV smaller ($n = 8$) or larger ($n = 7$) than 2.5 cm^3 for D_{Max} and D_{Mean} , see Fig. 3.4. For patients with a smaller CTV, the dosimetric advantage over SBRT was on average 0.9 Gy and 0.5 Gy lower for D_{Max} and D_{Mean} , respectively. This was associated with PTV_{PT} definition - the average volume ratio between PTV_{PT} and PTV_{SBRT} was 2.9 (1.6 - 4.0) and 1.5 (1.3 - 1.8), for patients with $\text{CTV} < 2.5 \text{ cm}^3$ and $\text{CTV} > 2.5 \text{ cm}^3$, respectively.

The 4 patients with multiple lesions were excluded from this comparison. The D_{Max} and D_{Mean} difference were on average higher in these patients, but the number of patients was too low for statistical analysis.

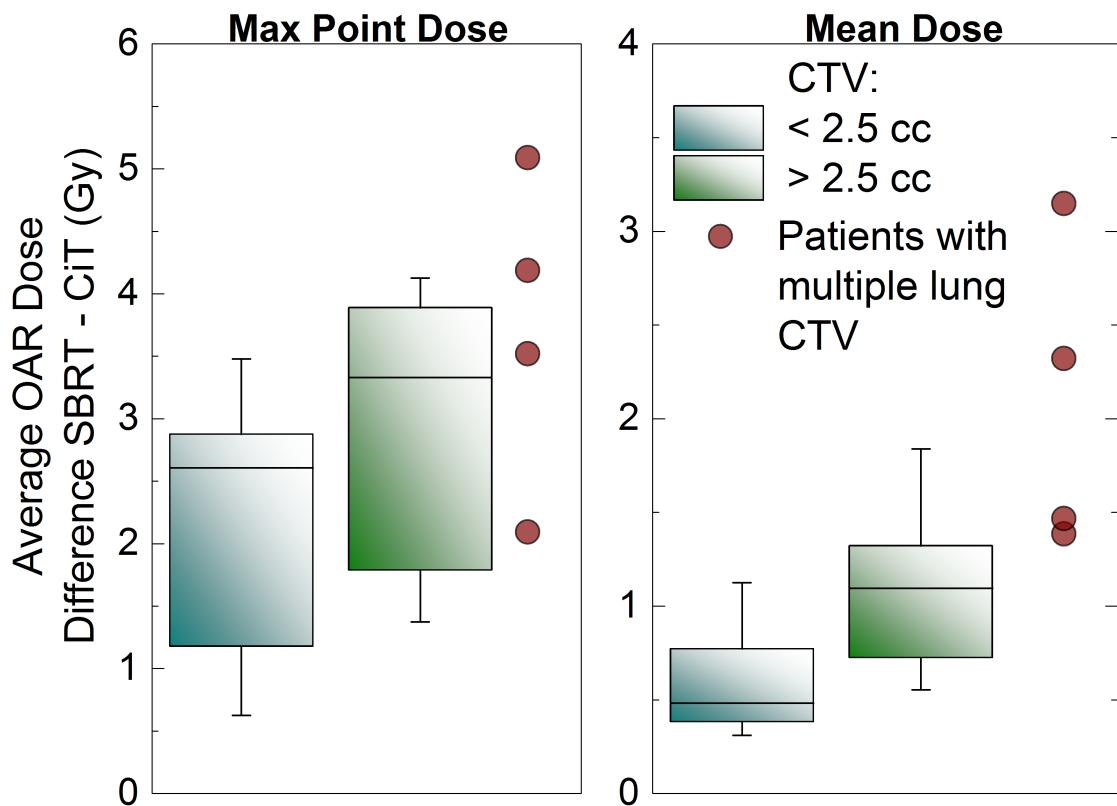


Figure 3.4: Box plots of average OARs max point dose (D_{Max}) and mean dose difference between SBRT and PT for patients with single CTV smaller ($n = 9$) or bigger ($n = 6$) than 2.5 cm^3 . Boxes represent 25% - 75%, outliers are shown as whiskers and median is shown with solid lines. Values for patients with multiple lesions are shown with circle symbols.

3.4 Discussion

This is the first in silico trial directly comparing clinically valid SBRT plans to scanned carbon ion plans using state of the art 4D dose calculation and motion mitigation methods for NSCLC patients. Our study found that PT deposited less dose to OARs compared to SBRT. Therefore PT might be considered as an alternative treatment option to SBRT. The finite range of the beam permits a small number of fields and thus a narrow entry channel, so that critical OARs such as spinal cord, heart, esophagus, and the contralateral lung could be effectively spared using PT, with typically low or even zero dose. PT could be thus highly beneficial to patients with impaired contralateral lung function, because PT deposited no dose in the contralateral lung in 12 patients, while SBRT irradiated the contralateral lung in all patients. Being an intensity-modulated arc therapy, SBRT had an advantage in some patients where the smaller airways were in a close proximity to CTV; SBRT could shape the dose distribution to reduce dose to the smaller airways, compensating PT's advantageous physical dose characteristics.

Further increase in OAR sparing could be achieved by using intensity modulated particle therapy (IMPT) instead of SFUD. While IMPT could lead to less dose in the OARs, it would make the plans less robust against setup errors due to additional dose gradients between the fields. These gradients can be controlled by employing robust optimization to account for range, motion and setup uncertainties, which we will implement in a future 4D treatment planning study [Chen et al., 2012, Graeff, 2014].

3.4.1 Range Margins and Motion Mitigation

Since conventional geometric margins are not suitable for PT [Park et al., 2012], margins based on range changes were used. Another trial comparing photon to proton therapy in NSCLC patients also used different PTV definitions to incorporate range changes [Roelofs et al., 2012]. As shown in our study, inclusion of range changes leads to increase in PTV_{PT} , up to 4.7 times compared to PTV_{SBRT} . Furthermore, the difference between PTVs is bigger for smaller tumor sizes. Patients with bigger tumor volumes ($CTV > 2.5 \text{ cm}^3$) are therefore better suited for treatment with PT.

Our results confirm previously published results that interplay can lead to a dose degradation in treating moving targets with active scanned beam [Bert et al., 2008]. Figure 3 shows the importance of using 4D dose calculation and motion mitigation techniques in treating moving targets with particles. Even small motion amplitude can lead to underdosage in CTV without proper motion mitigation. Considering the average over the 4 simulated motion patterns, 15 patients showed a $D_{99\%} < 24 \text{ Gy}$ under interplay conditions, as opposed to none when using rescanning (excluding the one patient with reduced target dose). Rescanning proved to be a strong mitigation technique, with robust results across all targets and different breathing patterns.

Recent studies suggest that some patients require phase-controlled layer or volumetric rescanning for sufficiently robust target coverage [Mori et al., 2013, Takahashi et al., 2014]. The advantage of simple slice-by-slice rescanning is that no motion monitoring or assumptions on the breathing frequency are necessary [Bert and Durante, 2011], but the higher required number of rescans might increase treatment times due to reduced beam intensities. Another possibility is to combine rescanning with gating, which was already successfully implemented in clinic [Rossi, 2016].

3.4.2 RBE and Proton Therapy

Carbon ions exhibit a radiobiological advantage, especially in the Bragg peak region. However, for high doses as used here the effect of RBE is not well documented and is subject to ongoing research [Friedrich et al., 2014]. For these high doses RBE for carbon ions should approach a

value between 1 and 2 [Carabe-Fernandez et al., 2007], which is in agreement with values in our study ($\tilde{1.1}$).

Coincidentally, RBE values in the target at high doses are similar to those used clinically in proton therapy. Carbon-ions show considerably lower lateral scattering though, which should result in even better OAR sparing than protons. Our results are in agreement with several in silico studies comparing SBRT and proton therapy for NSCLC [Roelofs et al., 2012, Kadoya et al., 2010, Register et al., 2010]. Furthermore, a study made by Kadoya reached the same conclusion as our study, that patients with larger CTV and/or multiple CTVs would receive less dose from proton therapy [Kadoya et al., 2010]. A recent phase II trial for patients with multiple sites of extracranial disease showed good results for photons [Iyengar et al., 2014], however, based on the findings of Kadoya et al and our study, proton and/or carbon-ion therapy might result in even better outcome.

3.4.3 Study limitations

The 4D dose calculations were based on a regular breathing pattern, which typically varies during patient treatment and/or between 4D-CT acquisition and actual treatment [Verma et al., 2010, Malinowski et al., 2011]. A possible solution was proposed by Boye et al. to get motion information from 4D magnetic resonance imaging (4DMRI) and use it in 4D dose calculations [Boye et al., 2013].

Furthermore, SBRT treatment plans were done on a static case in contrast to a 4D dose calculation done for PT. This should not influence the results of our study, since motion has a smaller impact on photon dose distributions [Zou et al., 2014], whereas it is imperative in PT dose calculations [Bert and Durante, 2011].

There were also differences in treatment planning. PT plans were done by a single person in a research setting, whereas SBRT plans were made by different people under clinical conditions with the requirement to finish the plans on time.

Slight changes also existed between the planning CT, used for SBRT treatment plans and 4D-CT used for PT treatment plans, even though 4D-CT was usually acquired right after the planning CT. The propagation of contours from the planning CT to the 4D-CT and also for the 4D dose calculation rely on deformable image registration (DIR), where even small changes can effect 4D dose distribution [Kashani et al., 2008]. Results from DIR were thoroughly checked and results were presented in Chapter 4. However, the transformation of the dose with DIR is a debated topic and might jeopardize the simulated results, especially with respect to the 4D target coverage. On the other hand, dose differences in OARs were large and should be robust against vector field errors in the order a few mm. Nevertheless, further studies are warranted, possibly using advanced moving phantoms for an experimental validation [Perrin et al., 2014] and finally also clinical trials. First patients are being treated in thoracic and abdominal regions

with an active beam scanning at the National Institute for Radiological Sciences (NIRS) in Japan [Mori et al., 2016].

3.4.4 Application

Scanned carbon ion therapy is available only in a limited number of clinics, mainly due to the considerably higher cost in comparison to photon linacs. Therefore a careful patient selection appears sensible. Patients with larger and multiple lesions where SDRT might be limited due to OAR constraints could be referred to carbon centers. In this study, already lesions larger than 2.5 cm^3 were found to benefit significantly stronger from CiT.

3.5 Conclusion

SBRT and PT both achieved satisfactory target dose. In most patients PT deposited less dose in all OARs (including heart, spinal cord, esophagus, trachea and aorta). Patients with multiple lesions and/or with large target volumes might be preferentially selected for particle therapy.

4 Treatment Planning for Patients with Multiple Lung Disease Sites

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4.1 Introduction

Lung cancer is the leading cause of cancer-related death, with approximately 160 000 deaths in the U.S. in 2014 [Siegel et al., 2014]. More than half of all patients with lung cancer are diagnosed with stage IV non-small cell lung cancer (NSCLC) [Ramalingam and Belani, 2008, Iyengar et al., 2014]. Prognosis for stage IV NSCLC is poor, with only 12 months median survival after first line chemotherapy [Socinski et al., 2013].

Stereotactic body radiation treatment (SBRT) shows good results for treating NSCLC [Baumann et al., 2009, Fakiris et al., 2009, Grutters et al., 2010, Greco et al., 2011]. Furthermore, several studies have shown that SBRT can be used in the setting of limited metastatic disease [Rusthoven et al., 2009, Villaruz et al., 2012, Salama et al., 2012, Iyengar et al., 2014]. Passive scattering particle therapy has also proved as an effective treatment for NSCLC [Grutters et al., 2010, Tsujii and Kamada, 2012] and it could be considered an alternative to photon treatment.

It was shown in Chapter 3 that scanned carbon ions (PT) could also be used as a treatment modality for NSCLC. One of the conclusions of the study shown in Chapter 3 was that patients with multiple disease sites would especially benefit from PT compared to SBRT. However, limitations of this study were small number of patients (4) and single-field uniform optimization (SFUD) used in treatment planning. Since patients with multiple metastases present complex geometry, clinically acceptable treatment plans can not be created with SFUD. Intensity modulated particle therapy (IMPT), on the other hand, should get an adequate treatment plans.

An investigation of IMPT with state of the art 4D optimization for treating lung cancer patients with multiple disease sites was made. Treatment plans were generated with two different 4D optimization techniques and compared with SBRT plans, which were actually used for treating patients.

4.2 Materials and Methods

For creation of treatment plans 4D extension of GSI's treatment planning system TRiP98 [Krämer and Scholz, 2000, Richter et al., 2013] was used and modified. A description of modifications and tools used will be given here, alongside with patient data.

4.2.1 Patient data

In this study, 8 patients with 2 - 5 lung metastases summing to 24 metastases in total were included. The lesion size was 4.2 cm^3 (median, 25-75% 2.4 - 22.2) and peak-to-peak motion was 5.9 mm (2.7 - 8.1). Details are given in Table 4.1. Target motion and PT treatment planning were based on a 4D-CT, consisting of 10 phases (0 - 9), with phase 0 (end-inhale) chosen as a reference phase. A registered positron emission tomography (PET) scan was used to delineate clinical target volumes (CTV).

Patients 1 - 4 had no OARs in CTV vicinity (closer than 10 mm) and patients 5 - 8 had at least one OAR in CTV vicinity (closer than 10 mm).

Patients were treated with SBRT at Chamaclimaud Center for the Unknown, Lisbon (Portugal), with different fraction schemes. Number of fractions and doses delivered are given in Table 4.1.

4.2.2 Multiple targets

The TRiP98 optimization works on minimizing residual of a nonlinear equation system [Krämer and Scholz, 2000]. The minimizing function $E(\vec{N})$ for particle number \vec{N} goes as:

$$E(\vec{N}) = \sum_{i \in T} \left(D_{pre}^i - D_{act}^i(\vec{N}) \right) = \sum_{i \in T} \left(D_{pre}^i - \sum_{j=1}^n c_{ij} N_j \right) \quad (4.1)$$

For a CT voxel i in target T , D_{pre} and D_{act} are the prescribed and the actual dose, respectively. The coefficient c_{ij} stands for correlation between dose deposition and field position j at a voxel i , with n the number of fields. There is no restriction for the number of targets or fields in the minimizing function, so it can be expanded to:

$$E(\vec{N}) = \sum_T \sum_{i \in T} \left(D_{pre}^i - \sum_{j=1}^n c_{ij} N_j \right) \quad (4.2)$$

However, the setup of raster points in TRiP98 allowed only one target. It was therefore expanded in a way that a field was designated to a specific target, as displayed in Fig 4.1.

Raster points for each field are created only around designated target. Contribution from all fields are then calculated in optimization. When a field from one target contributes dose to the other target this is taken into account in optimization function, specifically in coefficient c_{ij} in Eq. 4.3. Because the optimization function was not changed, all TRiP98 4D functionalities could be used, as explained in next sections.

Table 4.1: Target characteristics, with CTV volumes, peak-to-peak motions, fractionation schemes and number of fields used for PT treatment planning. Last column shows an OAR in target vicinity (closer than 10 mm), if present. SA stands for smaller airways and esoph. for esophagus.

Patient	Target	Volume (cm ³)	Peak-to-peak motion [mm]	Fractionation scheme	Number of fields	OAR in proximity
1	a	10.2	3.4	1 x 24 Gy	2	SA
	b	14.4	2.8			
2	a	2.3	12	1 x 24 Gy 5 x 7 Gy	2	
	b	0.4	11.8			
3	a	3.8	5.8	1 x 24 Gy	2	
	b	4.3	0.8			
	c	2.7	3.4			
	d	3.1	2.1			
	e	0.5	0.5			
4	a	139	0.6	1 x 24 Gy	3	
	b	9.2	2.0			
5	a	4	9	3 x 9 Gy 1 x 24 Gy	5	SA, esoph., heart
	b	0.8	7.8			
6	a	3.4	5	1 x 24 Gy	3	Heart
	b	2.4	4.4			
	c	2.0	6.3			
	d	2.4	6.4			
7	a	20.6	7.4	1 x 24 Gy	4	SA
	b	27.1	6.0			
8	a	136	12	3 x 9 Gy 1 x 20 Gy	2	Heart
	b	12.4	2.5			
	c	123	14	3 x 9 Gy 1 x 22 Gy	3	Heart
	d	80.7	17			
	e	86.7	6.6	1 x 20 Gy	3	SA

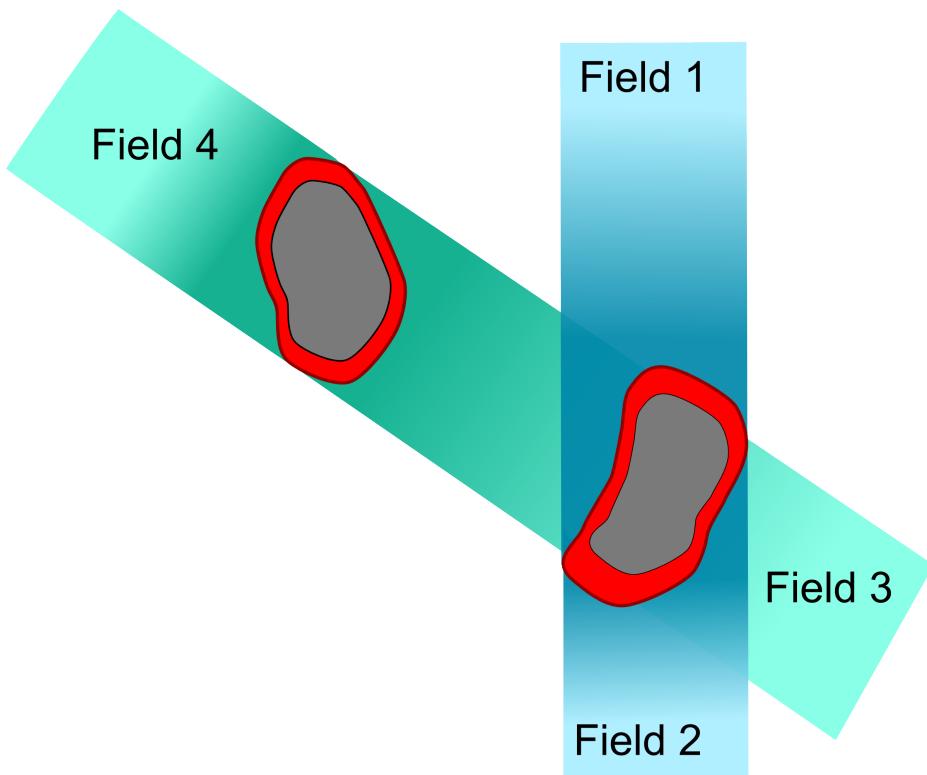


Figure 4.1: Multiple targets irradiation. Fields 1 and 2 are designated to target a and fields 3 and 4 to target b. Optimization takes into account all target voxels and contributions from all fields.

4.2.3 Optimization techniques

Investigation of two different optimization techniques to handle range changes in moving tumors was made. For each patient, two sets of plans were created: field-independent ITV (indITV) and 4D optimization (4Dopt).

- **Field-independet ITV:** A water-equivalent path length ITV (WEPL-ITV) is different for each field, creating unnecessary margins when combining WEPL-ITV from different fields (see Fig. 4.2a). Graeff et. al [Graeff et al., 2012] proposed a solution to include range margin into the field description itself, instead of creating a bigger PTV. Thus, no unnecessary margins are created. Treatment plans were made for all targets with intensity IMPT on a indITV in reference phase.
- **4D Optimization:** IMPT with indITV can produce inhomogeneous fields that yield homogeneous dose but only in reference phase. The WEPL can change in different motion phases, leading to inhomogeneous dose. 4Dopt uses WEPL-ITV for raster setup, however the actual optimization is performed on each target voxel in each motion state k . The optimization function thus changes to [Graeff et al., 2012]:

$$E(\vec{N}) = \sum_{k=1}^m \sum_{T_k} \sum_{i \in T_k} \left(D_{pre}^i - \sum_{j=1}^n c_{ijk} N \right) \quad (4.3)$$

All targets were treated with IMPT and 4D optimization. A subset of motion states 0, 5 and 7% was used for targets 6a - d, 7b, 8a and 8c due to large optimization problem - beside multiple targets, OAR was also included in motion states [Graeff et al., 2012].

The same number of fields and the same field angles were used in both techniques.

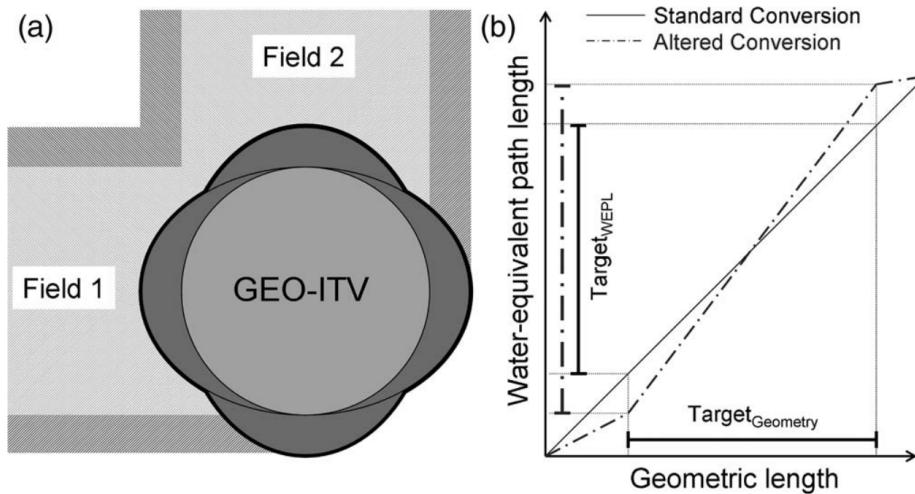


Figure 4.2: Schematic presentation of the indITV. (a) Dark gray ellipses show margins needed for specific fields to account for range changes in different motion states. When common target volume for two perpendicular fields is generated (this black contour) it creates unnecessary lateral extension of both fields, as shown by the dark gray entry channels. A solution is shown in (b). Rather than using standard, geometric, margins, both fields use the same geometry, however the conversion of geometry to WEPL is altered for each field. The plot in (b) shows the standard (solid line) and an altered conversion (dashed-dotted line) for a beam passing a homogeneous CTV. The altered conversion increases the WEPL extent and thus implicitly increasing margins for a single field only. Figure taken from [Graeff et al., 2012]

4.2.4 Treatment planning

An isotropic margin of 3 mm was added to each CTV to account for uncertainties in treatment delivery. An WEPL-ITV was constructed on the CTV with margins for each individual field, which was then used either in optimization (inITV) or for raster setup (4Dopt). Due to large memory demands, targets in each lung were optimized separately.

The objective for target was 99% of each target volume should receive at least 100% of the planned dose ($D_{99\%} \geq 100\%$). Furthermore, the doses to the OARs should be under the limits given by the AAPM task group [Benedict et al., 2010].

After the optimization 4D-dose was calculated for two motion periods (3.6 sec and 5.0 sec) and two starting phases (0° and 90°) as explained in Section 3.2.4. Motion was mitigated with five slice-by-slice rescans that were applied to each plan.

Detailed explanation of SBRT treatment planning is given in Section 3.2.3.

For patients 5 - 7 OAR dose could not be sufficiently reduced in optimization. It was necessary to add margins to the OAR and then subtract the OAR plus margins from the target. For SBRT the OAR plus margins was subtracted from PTV, while in PT it was subtracted from CTV plus 3 mm margin in all 9 motion states.

4.3 Results

Example of different treatment plans for patient 8 is shown in Fig. 4.3.

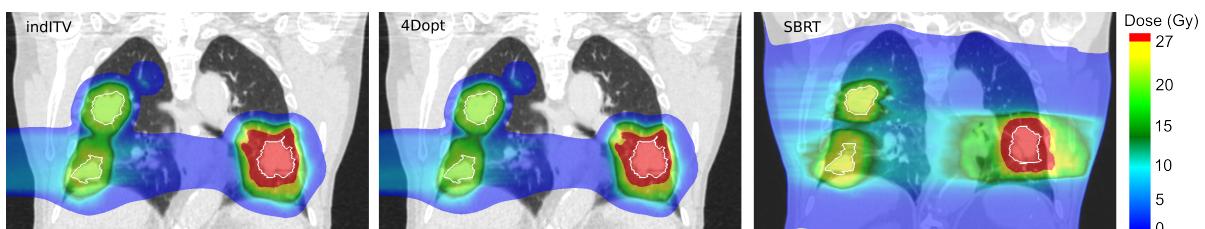


Figure 4.3: Treatment plans for indITV (left), 4Dopt (middle) and SBRT (right) for SBRT (solid lines) for patient 8. CTV contours are outlined in white.

4.3.1 Target Coverage

Results for CTV $D_{99\%}$ for all patients are shown in Table 4.2. All SBRT plans were approved by a physician, even though the prescription dose for patients 5 - 7 was not met due to an OAR proximity. Excluding patients 5 - 7, there were 8 cases (out of 20) of too low CTV dose across different motion types for indITV and 4Dopt, respectively. The lowest CTV $D_{99\%}$ was 86.5%. For patients 6 - 8 indITV and 4Dopt had higher CTV $D_{99\%}$ than SBRT, except for target 7c. There was no significant difference in CTV $D_{99\%}$ between SBRT, indITV and 4Dopt.

Table 4.2: CTV $D_{99\%}$ for indITV, 4Dopt and SBRT for 8 patients. Results for indITV and 4Dopt are shown as median (range) across different motion types.

Patient	Target	CTV $D_{99\%}$ (%)		
		indITV	4Dopt	SBRT
1	a	101.6(100.0 - 102.1)	101.0(101.0 - 101.0)	100.0
	b	101.6(101.0 - 102.1)	102.1(101.0 - 102.1)	100.0
1	a	101.0(100.0 - 101.0)	100.5(100.0 - 101.0)	101.0
	b	107.1(103.6 - 107.1)	100.0(100.0 - 103.6)	100.0
1	a	101.0(99.0 - 102.1)	99.0(99.0 - 102.1)	106.3
	b	102.1(99.0 - 102.1)	102.1(102.1 - 102.1)	103.1
	c	101.0(101.0 - 102.1)	101.6(101.0 - 102.1)	104.2
	d	102.1(99.0 - 102.1)	101.6(101.0 - 102.1)	107.3
	e	102.1(102.1 - 102.1)	102.1(101.0 - 102.1)	108.3
1	a	102.1(102.1 - 102.1)	102.1(102.1 - 102.1)	101.0
	b	99.0(99.0 - 99.0)	100.0(100.0 - 101.0)	102.1
1	a	64.4(63.9 - 64.8)	74.5(74.1 - 75.9)	66.7
	b	100.5(99.0 - 102.1)	100.5(99.0 - 102.1)	103.1
1	a	100.5(100.0 - 102.1)	99.5(99.0 - 101.0)	101.0
	b	100.5(100.0 - 101.0)	100.0(100.0 - 100.0)	101.0
	c	91.1(88.5 - 92.7)	92.7(86.5 - 93.8)	99.0
	d	97.4(93.8 - 100.0)	100.0(99.0 - 101.0)	94.8
1	a	87.5(86.5 - 89.6)	94.3(92.7 - 94.8)	69.8
	b	79.7(79.2 - 81.3)	78.6(77.1 - 79.2)	69.8
1	a	100.9(100.0 - 100.9)	99.5(99.1 - 100.9)	105.6
	b	100.0(98.8 - 101.3)	102.5(101.3 - 102.5)	105.0
	c	99.1(99.1 - 100.0)	99.5(97.2 - 100.0)	106.5
	d	102.3(100.0 - 104.5)	100.6(100.0 - 101.1)	102.3
	e	101.9(101.3 - 102.5)	102.5(101.3 - 102.5)	101.3

4.3.2 Dose in OARs

D_{Max} and D_{Mean} for 8 OARs are shown in Table 4.3. There was a significant difference between PT and SBRT in D_{Max} and D_{Mean} for heart, spinal cord, esophagus and aorta and in D_{Mean} for smaller airways and ipsilateral lung. No significant difference was observed in dose to OAR between different motion types or between indITV and 4Dopt. The overall OAR difference for patients between SBRT and mITV was significant, 3.1 Gy (0.5 - 7.9) for D_{Max} and 1.7 Gy (0.7 - 3.0) for D_{Mean} . There was no significant difference between mITV and 4DITV to overall dose to OAR. The ipsilateral lung $V_{20\%}$ was 14.4 (0.0 - 43.0), 14.6 (0.0 - 41.4) and 29.8 (5.8 - 89.2)% for mITV, indITV and SBRT, respectively. Both, mITV and 4DITV ipsilateral lung $V_{20\%}$ was significantly different from SBRT, while no significant difference was observed between mITV and 4DITV.

Dose volume histograms (DVH) for patients 5 - 8 are shown in Fig. 4.4. The margins used for OAR subtraction for PT and SBRT, respectively, were: 3 and 5 mm for smaller airways, 0 and 1 mm for esophagus in patient 5; 0 and 2 mm for heart in patient 6; 2 and 11 mm for smaller airways in left lung, 0 and 9 mm for smaller airways in right lung.

All treatment plans exceeded the D_{Max} limit for smaller airways in patients 5, 7 and 8 and for heart in patient 7. Additionally, SBRT Esophagus and Heart D_{Max} limits were exceeded in patients 5 and 8, respectively.

Table 4.3: OAR D_{Max} and D_{Mean} of all patients for indITV, 4Dopt and SBRT. There was significant difference between PT and SBRT for all OARs, except smaller airways' D_{Max} . Data is displayed as median (range).

OAR	indITV	4Dopt	SBRT
D_{Max} (Gy)			
heart	13.9(0.0 - 28.5)	14.6(0.0 - 29.3)	18.1(7.5 - 30.5)
spinalcord	0.4(0.0 - 8.3)	0.3(0.0 - 8.5)	9.0(3.0 - 12.5)
smallerairways	11.6(0.0 - 21.3)	11.5(0.0 - 22.8)	15.6(0.0 - 22.8)
esophagus	0.6(0.0 - 23.0)	0.9(0.0 - 23.3)	11.5(5.5 - 25.5)
aorta	4.4(0.0 - 28.5)	6.3(1.5 - 26.5)	18.1(6.3 - 31.0)
Ipsilateral lung	26.6(0.0 - 31.5)	26.1(0.3 - 29.8)	26.1(3.8 - 32.3)
D_{Mean} (Gy)			
heart	0.3(0.0 - 0.8)	0.4(0.0 - 0.8)	4.4(2.5 - 10.1)
spinalcord	0.0(0.0 - 0.5)	0.0(0.0 - 0.6)	1.8(0.8 - 2.5)
smallerairways	1.1(0.0 - 5.6)	1.2(0.0 - 7.3)	3.5(0.0 - 7.5)
esophagus	0.1(0.0 - 1.3)	0.1(0.0 - 1.4)	3.3(1.4 - 5.1)
aorta	0.3(0.0 - 1.0)	0.4(0.0 - 0.8)	2.9(1.3 - 6.2)
Ipsilateral lung	2.2(0.0 - 9.1)	2.3(0.0 - 8.6)	4.1(0.8 - 10.5)

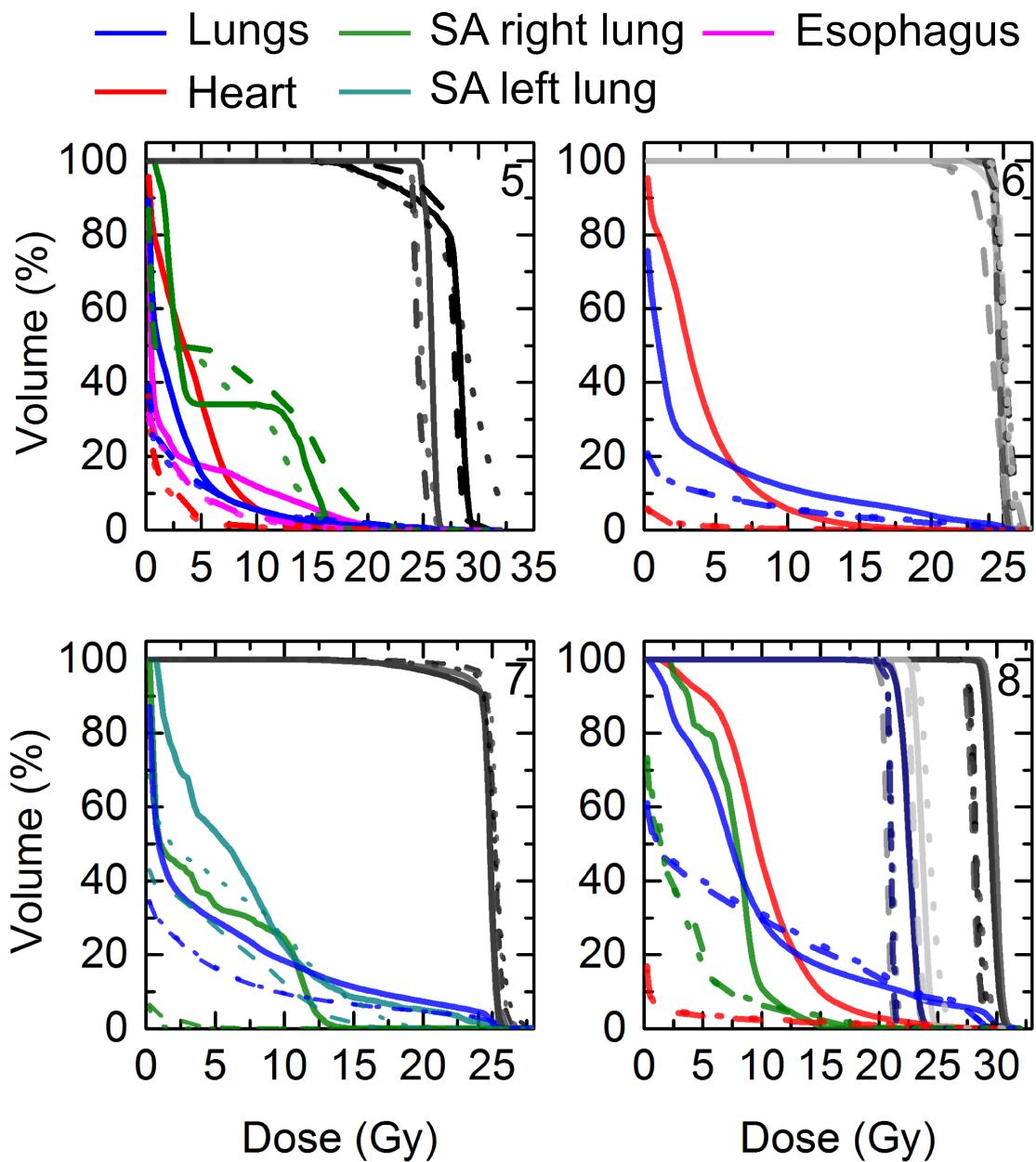


Figure 4.4: Dose volume histograms for patients 5 -8. SBRT, mITV and 4DITV are represented by solid, dashed and dotted line, respectively. Targets are displayed in grayscale, while OAR use colors shown above. SA stands for smaller airways.

4.4 Summary and Discussion

Clinically valid SBRT plans have been compared to PT treatment plans for NSCLC patients with multiple metastases. To the best of our knowledge, this is the first study of treating multiple NSCLC metastases with PT. Novel approach was used to handle multiple targets, together with the state of the are 4D PT treatment planning. Furthermore, 4D PT doses were calculated for different motion types.

PT on average delivered less dose to OAR, while still having comparable target coverage. The most apparent difference is in lung $V_{20\%}$, which was on average half the value with PT compared to SBRT. For patients with complex geometry (5 - 8) PT maintained or even improved target coverage in most cases, while reducing doses to OARs. The exception were smaller airways in patients 5, which receive more dose, but the CTV $D_{99\%}$ patient 5 was improved. Additionally, margins used for OAR subtraction were smaller in PT, resulting in better CTV coverage.

There was no significant difference between indITV and 4Dopt in target coverage or in dose to OAR. However, in patients 5 and 7 the 4Dopt was able to achieve better target coverage. With indITV, patient 5 had extreme inhomogeneous target coverage, resulting in lung $D_{Max} = 32.5$ Gy, compared to 29.3 Gy and 29.8 Gy with 4Dopt and SBRT, respectively. For patient 7, 4Dopt deposited less dose to smaller airways in addition to better target coverage.

Even though PT deposits less dose to OAR with the same or even better target coverage, there is still room for improvement in PT 4D treatment planning. An implementation of multi-criteria objective planning should bring even better dose distribution and bring possibility to choose between trade-offs [Breedveld et al., 2007, Chen et al., 2010]. Additionally, multiple target optimization in PT would benefit from a shell around PT where dose would be minimized. Therefore excessive dose in healthy tissue would be further reduced. An introduction of a shell, however, would further enlarge the optimization problem, which is big already for complex geometry (patient 5 - 8). A possible solution for minimizing voxel number in optimization would be with adaptive dose grid [Prall1 et al., 2016].

In Chapter 3 additional range margins to account for range uncertainties could be used in treatment planning, due to SFUD. Because we did not use field specific PTVs it was not possible to include range uncertainties in our study. Instead of creating field specific PTVs to include range uncertainties, a solution was proposed to include uncertainties in optimization process itself [Pflugfelder et al., 2008, Unkelbach et al., 2009, Fredriksson et al., 2011, Chen et al., 2012]. Chen et al. have shown it is possible to implement robust optimization in multi-criteria optimization as well [Chen et al., 2012]. Furthermore, in a recent treatment planning study by Liu et al. [Liu et al., 2016b] a 4D robust optimization was demonstrated, with better results over 3D robust optimization for NSCLC patients. However, only breathing starting phase was used as an uncertainty, whereas different motion types should be considered.

The disadvantage of 3D and 4D robust optimization is the enlargement of the optimization problem.

Patient 6 D_{Max} heart dose ranged over 2 Gy across different motion types in 4Dopt, showing the necessity of making treatment plans robust against motion uncertainty, especially in the hypo-fractionated regimen. Furthermore, the doses to OARs that are under the limits after optimization, may exceed them after calculating 4D dose. The indITV and 4Dopt approaches take into account range changes in different motion states, however they do not guarantee 4D doses. This could be achieved with beam tracking [Bert and Rietzel, 2007], when each motion state has designated treatment plan. Clinical application of beam tracking is not yet feasible due to several reasons, such as the inverse interplay, the ion-beam tracking system complexity, precision and speed of the motion monitoring. Another solution would be jet-ventilation [Santiago et al., 2013], however, it brings additional complications to treatment.

Apart from 4D robust optimization, the effect of motion could be minimized by using other motion mitigation techniques, such as gating. Furthermore, gating could improve the target coverage, where the planned dose was not met. Gating, together with rescanning, has already been successfully implemented clinically for active beam scanning [Rossi, 2016, Mori et al., 2016] and it might be essential to use it in hypo-fractionated treatment of moving tumors.

A recent review showed good local control rates between 66 - 92% for patients treated with SBRT in reoccurred tumors in previous irradiation field [Amini et al., 2014]. However, there were grade 4 and 5 complications present, i.e. study by Trovo et al showed grade 5 pneumonia in 6% of patient treated [Trovo et al., 2014]. As shown in our study, PT delivers less dose to the OAR, ipsilateral lung in particular, and could hence reduce the number of treatment-related complications.

4.5 Conclusions

PT delivers less dose to OAR compared to SBRT in NSCLC patients with multiple disease sites, while maintaining the same target coverage. Caution has to be taken in patients with OAR in CTV vicinity (less than 10 mm), where doses to OAR differ across different motion types. No significant difference was found between two 4D optimization techniques. However, 4D optimization showed better results for patients with OAR in CTV vicinity.

5 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 OAR. 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. Additionally, a prospect for treating patients with multiple lung metastases was displayed.

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.

5.1 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., 2006b] 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 2.2.2, 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]. A B-Spline algorithm and mean square error metric 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]. However, a comparison between different algorithms and optimization metrics and their effect on DIRQA is warranted.

5.1.1 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 evaluation of vector field's mathematical properties. 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 were implemented in the scope of this thesis. 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 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 [?] 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 et al [Stanley et al., 2013]. They proposed a computational phantoms and their deformations with a finite element module framework. 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 and the effect of image downsampling on DIRQA should be assessed.

5.2 Radiation treatment for non-small cell lung cancer

5.2.1 Non-small cell lung cancer in early stages

Surgery is the gold standard for 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. A recent comparison study by Yu et al [Yu et al., 2015] showed that SBRT compared to surgery had lower intermediate mortality and toxicity. However, patients with long life expectancies were found to benefit more from surgery.

There are several clinical scenarios where the use of SBRT might be limited. This includes treatment of centrally located tumors, tumors close to the 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. 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 stressed, that this were patients were rejected from SBRT treatment due to complexity and regardless proton therapy achieved similar results to SBRT.

5.2.2 Non-small cell lung cancer in advanced stages

Treatment for early stage NSCLC is well established, however, 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 a recent phase 3 randomized trial by Bradley et al [Bradley et al., 2010], however, showed better survival rates for patients administered 60 Gy, instead of 74 Gy. It was speculated that higher doses to heart and esophagus might have contributed to higher mortality rates [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. For patients with multiple disease sites the the average mean heart and esophagus dose would be 4 and 3 Gy smaller. Similar results were observed when comparing protons to SBRT [Georg et al., 2008].

In a recent phase II study by Iyengar et al [Iyengar et al., 2014] they treated stage IV NSCLC 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 that stage IV NSCLC patients have 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 contralateral lung, whereas SBRT deposited dose in contralateral lung in all patients. The PT treatment planning for patients with complex geometry has to include 4D optimization and dose calculation as shown within this thesis. A special consideration has to be taken in dose to OAR limits, since they can be breached under different motion patterns. Beam tracking [Bert and Rietzel, 2007] or jet-ventilation [Santiago et al., 2013] would be possible solutions, however, the former is not yet clinically available and the latter significantly complicates treatment.

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.

5.2.3 Motion mitigation

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 maximum allowed point dose to OAR. In hypofractionated treatment this limit is strict and exact dose to OAR must be known. A possible solution would be to simulate rescanning and 4D delivery in optimization process itself. However such solution is not yet feasible due to the complexity of the problem.

Commonly used motion mitigation technique in photon and particle treatment is gating. 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. 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 is beam tracking the most precise technique, since it requires no internal margins for target [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 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.

5.2.4 Outlook

Recent advances in photon radiotherapy allow the usage of noncoplanar beams, a so-called 4π optimization [Dong et al., 2013b]. In a recent study, 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 short in PT, while the inclusion of uncertainties in optimization process can substantially improve treatment plans [Chen et al., 2012]. The robustness optimization is now possible even for a 4D optimization [Liu et al., 2016b], opening a wide field of new possibilities.



6 Conclusion

In this work, designated tools were developed to handle deformable image registrations on different image sets. Furthermore, several test were integrated to ensure quality assurance of the deformable image registration. The tools developed underwent an extensive testing on a large patient dataset and were able to produce deformable image registrations as well as find errors in it.

The deformable image registration was than used for 4D dose calculations of scanned carbon-ions treatment plans in lung cancer patients. The results were compared to state of the art photon treatment plans. With rescanning as a motion mitigation technique, carbon-ions were able to achieve the same target coverage as photon plans, while reducing the dose to critical structures including heart, spinal cord, esophagus, trachea and aorta.

For patients with multiple disease sites, a treatment planning system was modified to be able to create plans for such patients. Treatment plans for patients with multiple lung disease sites were generated with two recent 4D optimization algorithms. Both provided comparable target coverage to photon plans and lower doses to critical structures.



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Erklärung zur Dissertation

Hiermit versichere ich, die vorliegende Dissertation ohne Hilfe Dritter nur mit den angegebenen Quellen und Hilfsmitteln angefertigt zu haben. Alle Stellen, die aus Quellen entnommen wurden, sind als solche kenntlich gemacht. Diese Arbeit hat in gleicher oder ähnlicher Form noch keiner Prüfungsbehörde vorgelegen.

Darmstadt, den 15. Juni 2016

(Kristjan Anderle)

