\section{Discussion}

In this chapter the influence of heart beat motion on the PVs was studied and treatment planning studies with rescanning as motion

mitigation technique were carried out. A detailed analysis of the dose depositions to the OAR was performed, with special

emphasis on the irradiation of cardiac substructures. Beforehand, a study of the best suited field number and beam directions was

conducted as well as an analysis of possible safety margin limitations.

\subsection{Dose to critical structures}

\label{Discussion:doseOAR}

Concerning the dose deposition in OAR (esophagus, trachea, aorta and heart) dose-volume limits from SBRT were used. In SBRT

treatment of a high dose is also applied in a single fraction and hence comparable to the here stated dose delivery of 25Gy physical

dose in one treatment session.

An extensive collection of dose-volume-limits for SBRT are presented in the study protocols of the Radiation Therapy Oncology Group (RTOG).

The trachea (10.5Gy in 4cm$^{3}$) and aorta (31Gy in 10cm$^{3}$) dose-volume limits were not exceeded for any of the studied field

numbers and beam channel combinations. The same is valid while keeping the chosen three fields (couch angle of 90$^{\circ}$

and gantry angles of -45$^{\circ}$, 135$^{\circ}$ and 0$^{\circ}$) constant and changing the studied safety margins (0mm, 3mm, 5mm and 7mm).

For the esophagus on the other hand, the dose-volume limits are much more critical. Most of the studied beam directions yielded a dose

which exceeded the stated dose-volume limit (11.9Gy for 5cm$^{3}$). Hence an IMPT delivery, including the esophagus in the

optimization process, was necessary. With this delivery technique and the above stated beam direction, the dose to the esophagus could be

drastically reduced,. Nevertheless only an irradiation of the PVs with 3mm safety margin resulted in a dose deposition into the esophagus

which met the dose volume limit (median of 9.25Gy, 75th percentile: 12.13Gy). This result could be drastically improved with different IMPT

parameters, enabling a safe irradiation when patient specific IMPT parameters were used.

Thus also safety margins higher then 3mm should result in a uncritical dose deposition.

For the heart all beam channels, safety margins and delivery types (ITV or IMPT) exceeded the stated dose-volume limit (16 Gy for 15cm$^{3}$).

This is due to the fact that the heart is not only an OAR in the here presented, non-invasive treatment modality for PV isolation,

but part of the cardiac structures are also the target itself. Hence a closer look on the affected cardiac substructures and

the relevance of these dose depositions on cardiac toxicity and late effects were given.\newline

\newline

QUANTEC (quantitative analysis of normal tissue effects in the clinic) \cite{QUANTEC10} offers an comprehensive literature review

on the available data of the last 20 years and is meant as an update of the extensively used dose-limits proposed by Emami et al.

\cite{Ema91}. In the QUANTEC publication by Gagliardi et al. \cite{Gag10} radiation dose-volume effects in the heart are presented.

It is stated that radiation-induced cardiac diseases are distinguished between acute injuries like pericarditis\footnote{inflammation

of the sac containing the heart}, which can turn into a chronic disease, and late injuries which manifest months or even

years after radiation exposure. Typical late injuries are congestive heart failure\footnote{heart is unable to maintain sufficient

blood flow}, ischemia\footnote{deficient blood supply}, coronary artery disease and myocardial infarction\footnote{heart attack}.

It was summarized that it remains uncertain which region of the heart is most important for radiation induced tissue toxicities.

But it is stated that the risk of cardiac events is probably related to both dose and irradiated volume.

Pericarditis seems to be related to left ventricle (LV) irradiation, and it was found that LV shielding was able to drastically

reduce the incidence rate \cite{Carm76}. It was stated that a mean cardiac dose of 27.1 Gy and maximum dose of 47 Gy seem to act as

predictors for pericarditis \cite{Mar98}.

% and a fraction size of smaller than 3.5 Gy per fraction did not result in pericarditis.

Wei et al. \cite{Wei08} stated another discriminator for pericarditis which was found to be V30 < 46\%, which translates in a mean

pericardial dose of less than 26 Gy. For coronary and ischemic events relevant substructcm$^{3}$ures are assumed to be coronary arteries on

the left ventricle (LCA) \cite{Nie07} \cite{Tay07} \cite{Tay08}. Furthermore it is stated that excess deaths from heart disease are observed

in patients receiving more than 42 Gy \cite{Han93} and that aortic and mitral stenosis incidences increased above a threshold dose of

30 Gy \cite{Tay07}. For long term cardiac mortality an increased rate was only observed at whole heart doses above 30 Gy \cite{Han93}.\newline

\newline

Hooning et al. \cite{Hoo07} studied the cardiovascular disease incidence in more than 4000 breast cancer survivors

after a follow-up period of more than 10 years as patients were treated from 1970 through 1986. It was the first study to examine the

effects of cardiovascular risk factors in combination to radiotherapy. They found that the risk of congestive heart failure was

significantly increased when the patients had received chemotherapy (95\% confidence interval of 1.25 to 2.73) and that smoking drastically

increased the risk of the patients to suffer a myocardial infarction (95\% confidence interval of 2.03 to 4.55). Concerning

radiotherapy they stated that a higher mean dose to the whole heart resulted in an increased risk of congestive heart failure and

that an irradiation of the left vs right chest wall (thus more heart volume and in particular including the LV and apex) led to an

increased risk of myocardial infarction.\newline

\newline

A recent study by Darby et al. \cite{Dar13} investigated more than 2000 breast cancer patients treated in between 1958 and 2001

for coronary events like myocardial infarction, coronary revascularization or death from ischemic heart disease. The found a mean

heart dose of 4.9 Gy (0.03 Gy to 27.72 Gy) and that the rates of major coronary events increased linearly with the mean heart dose.

They stated an increase of incidences by 7.4\% per Gy (95\% confidence interval of 2.9 to 14.5) after five years post radiotherapy.

\newpage

For the here studied seventeen beam channel combinations, applying a physical dose of 25Gy, the mean dose over all five studied patients was

found to have a median of 1.26Gy (75th percentile: 1.48Gy). The median over the maximal point dose was 26.60Gy (75th percentile: 27.12Gy),

while in general less than 30\% of the heart was irradiated. With the chosen field number of three beam channels with directions of a

couch angle of 90$^{\circ}$ and gantry angles of -45$^{\circ}$, 135$^{\circ}$ and 0$^{\circ}$, the mean dose was found to less than 2Gy in all

studied patient cases. For different added safety margins to the PVs it was found that the median mean dose over all patients was

0.97Gy (75th percentile: 1.12Gy) with no margin, 1.26Gy (75th percentile: 1.48Gy) for 3mm, 1.43Gy (75th percentile:1.59Gy) for 5mm and

1.54Gy (75th percentile: 1.63Gy) for 7mm margin. Hence, all these results are in good agreement to the dose and volume limitations

stated in the above studies and thus no pericarditis should be expected when irradiating the PVs with an IMPT

delivery of carbon ions.

As the LV, and with it especially the LCA, are assumed to be radiosensitive structures within the heart the dose

depositions to these structures were analyzed in more detail. It was found that three beam channel directions were best suited to yield a lower

mean dose deposition in the LCA. Due to robustness criteria of the treatment delivery the above stated beam channel combination was

chosen. With this delivery direction it was found that the mean dose to the LCA was, dependent on the used safety margin, 0.22 Gy(75th

percentile: 0.54Gy) with no margin, 0.46Gy (75th percentile: 0.46Gy) for 3mm margin, 0.69Gy (75th percentile: 1.13Gy) for 5mm and

1.45Gy (75th percentile: 1.58Gy) for 7mm. The maximum point dose to the LCA with these beam channels nevertheless led to

an increased dose in the left chamber compared to the right site. This is due to the proximity of the upper LCA branches

to the LPV target site.

\subsection{Beam channel directions and safety margins}

In general, it can be stated that field number and beam direction always result in a trade-off between dose to the OAR, irradiation time and

robustness. While less fields and hence beam directions shorten the treatment time, it does lead to a less robust treatment. In case OAR are

displaced during the treatment (intrafractional motion, see Introduction) or move in between CT image acquisition and irradiation

(interfractional motion) beam channels with a large angle in between them are more robust, as not all fields are affected by this displacement

and hence only a small dosis would be shifted. Furthermore, opposite fields (like -45$^{\circ}$ and 135$^{\circ}$ (see figure

\ref{gantrydirection}) are more robust against potential range uncertainties and should hence be favored. Due to this reason, combined with

the smaller LCA dose deposition in case of three field numbers, a couch angle of 90$^{\circ}$ and gantry angles of -45$^{\circ}$,

135$^{\circ}$ and 0$^{\circ}$ was selected for the safety margin limitation studies as well as the motion mitigation treatment plans.

Concerning safety margins, which need to be applied in order to account for possible deviations in between treatment planning and dose

delivery, it can be stated that only a small margin tolerance was observed. This is due to the difficult position of the PVs close to

radiosensitive structures like the esophagus and especially the heart. With IMPT treatment a delivery with 3mm safety margin was found to

fulfill all the needed requirements. A more realistic safety margin of 5mm could be achieved with more restricted parameters in the IMPT

optimization.

\subsection{Movement of PVs in cardiac cycle}

Lickfett et al. \cite{Lic05} analyzed the volume changes and displacement of the PVs in 25 healthy volunteers with MRI images. They

studied the posterior edge of the PV orifice and observed that the size and location changed considerably during the cardiac cycle.

Displacements of up to 7.2 mm were found and it could be concluded that the motion amplitudes were bigger in the coronal (left-right)

than in the sagittal (anterior-posterior) direction. In more detail this largest coronal movement was found in the left superior PV,

while the largest sagittal motion was observed in the right superior PV with 3.9 mm. The smallest saggital displacement was 2.5 mm in the

left anterior PV. They suspected that the reason for movement is not resulting from a single influence, but is rather a mix of PV

contraction, atrial contraction and ventricular force. The movement of PV due to heartbeat is also relevant for catheter ablation. Based

on the stated finding Lickfett et al. recommended to keep a 5 mm distance from the PV orifice during PV encircling ablation in order to

reduce the risk for PV stenosis.

Patel et al. \cite{Pat08} on the other hand, who studied the MRI images of 30 patients in sinus rhythm with paroxysmal atrial fibrillation,

stated that the displacement of the pulmonary veins was small. The left lower PV was found to move (2.7 $\pm$ 1.2) mm, the left upper PV

(2.1 $\pm$ 1.1) mm, the right lower PV (1.9 $\pm$ 1.1) mm and the right upper PV (2.3 $\pm$ 1.0) mm.\newline

\newline

In the here studied patient cohort of five AF patients no differentiation between the upper and lower PVs was carried out.

The motion was assessed for the whole potential ablation site of LPV and RPV, respectively. Similar to the study by Patel et al. only a small

displacement was found, resulting to an average absolute displacement of less than 3mm (LPV: (2.71 $\pm$ 1.57)mm, RPV: (2.62 $\pm$ 1.41)mm).

Even though a tendency to a higher motion in AP direction could be observed, the contributions of the other motion directions

were in the same order of magnitude (up to 1mm). Hence no dominant motion direction could be determined.

The motion phases of the heartbeat gated CT scan h are based on the ECG trace and result in a division of a single heartbeat. Thus the motion

phases can be directly assigned to the contraction (systole) and dilatation (diastole) of both atria and ventricles.

Nevertheless no motion phase could be assessed to yield the maximum displacement. This reinforces the thesis by Lickfett et al. that the

underlying heartbeat motion, which causes the PVs to move, is much more complex.

\newpage

\subsection{Rescanning as motion mitigation technique}

Concerning dose deposition with rescanning compared to interplay iy can be concluded that rescanning yields good result.

Regarding dose coverage V95 values were higher than 99\% in 96.25\% of all studied cases with a safety margin of 3mm or higher.

The minimum dose coverage over all studied cases with safety margin was found in patient 1, in the irradiation of the LPV with a margin

of 3mm and an underlying motion of 1s period and 90$^{\circ}$ starting phase (V95=93.18\%). This result was obtained with five rescans.

With higher rescans the dose coverage could be improved, so that only 1.46\% of the studied cases with ten or more rescans had a dose coverage

smaller than 99\% (minimum: 97.11\%; 10 rescans in patient 1, 7mm safety margin and motion of 1s period and 90$^{\circ}$ starting phase).

The dose coverage for rescans without safety margin was worse, resulting in 93.12\% cases under 99\%.

V107 values higher than 0\% were obtained in 7.29\% of all cases with safety margin (maximum of V107=3.71\% in the LPV of patient 3

with safety margin of 5mm, 5 rescans and motion of 1s period and 0$^{\circ}$ starting phase) compared to

28.75\% of cases without safety margin (maximum: V107=7.99\% for the LPV of patient 2 with 5 rescans and motion of 1s period

and 0$^{\circ}$ starting phase. This could be reduced to V107=2.87\% with 10 rescans). With safety margin, the dose homogeneity D5-D95

did not exceed 8.9\%. Without safety margin D5-D95 did not exceed 10.2\%. Both of these values were achieved with 5 rescans and could be

improved with 10 rescans (with safety margin to less than 7\% and without to less than 9\%). It can hence be concluded that additional

safety margins enable a more robust and successful treatment delivery. However, if possible, these margins should be kept as small

as technical feasible, as it increases the dose deposition in OARs. Regarding rescan numbers ten rescans yield improved results compared

to five rescans. These result are not significantly improved with higher rescan numbers.

\section{Conclusion}

Rescanning yields improved dose coverage and dose homogeneity compared to interplay in all studied patient cases, motion patterns and

for all safety margins. It is thus an adequate motion mitigation technique for the irradiation of PVs under influence of heart beat motion.

A rescan number of ten is sufficient to obtain results comparable to the static irradiation.

For the treatment delivery, IMPT dose optimization together with a rather small safety margin (of e.g. 3mm) results in dose depositions in the

OARs (like esophagus as well as in the cardiac substructures) which are considered tolerable.