4DMRI-based analysis of inter— and intrafractional pancreas motion and deformation with different immobilization devices

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Abstract

Time-resolved magnetic resonance imaging (4DMRI) provides spatial motion information with high soft-tissue contrast. This study exploits the potential of 4DMRI by investigation of inter- and intrafractional pancreas motion and deformation with different patient immobilization devices. In total, 150 4DMRI scans were acquired for a cohort of 5 volunteers, each was scanned in 10 imaging sessions using three different positioning modes (flat table top (FTT), vacuum bag (VB), abdominal corset (AC)), respectively, to simulate repeated 4DMR imaging sessions of patients during fractionated radiotherapy. Large pancreatic motion variations were observed throughout the volunteers with mean inferior-superior (IS) motion amplitudes up to 28.5/21.9 mm for FTT/VB measurements, which were reduced by 48%/34%, respectively, by using abdominal corsets. Small IS motion reductions were present for vacuum bag measurements, compared to flat table top measurements. Corset measurements additionally showed an improved motion reproducibility between different days by more than 60% compared to FTT and VB. In anterior-posterior direction, motion amplitudes were reduced by 69%/60% for corset measurement, compared to FTT/VB, and their day-to-day fluctuations were reduced by approximately 130%. With respect to respiration-induced pancreas deformations, the pancreas showed the lowest deformation and highest reproducibility for corset measurements in 4 out of 5 volunteers. Moreover, both, the VB and AC setup showed a generally improved setup reproducibility compared to the non-immobilized flat table top setting. All in all, in this study, abdominal corsets showed to reduce both pancreatic motion and deformations. Moreover, by using corsets it is possible to improve the reproducibility of both pancreatic motion and deformation, which are important factors in radiotherapy treatments. Therefore, radiotherapy treatments of pancreatic cancer patients with abdominal corsets may be a viable option for patients with large internal organ motion amplitudes and may lead to a better consistency of the treatment planning and delivery situation.
1. Introduction

Radiotherapy treatments with highly localized dose in the tumor region and sparing of healthy surrounding tissue are very challenging for pancreatic cancer due to many adjacent organs (stomach, bowel, duodenum, kidneys, spleen) with limited tolerance doses and significant motion and deformation. Particle therapy, providing highly focused and spatially accurate particle beams, offers a promising possibility for improvements of clinical outcomes for pancreatic cancer patients (Terashima et al, 2012, Shinoto et al, 2013, Durante et al, 2015). However, the advantage of a better dose conformity to the target, as offered by the Bragg-peaks of particle beams when compared to photons, is partly counteracted by both intrafractional and interfractional anatomical changes (Lomax et al, 2008). Intrafractional respiration-induced motion for instance may lead to interplay effects and consequently to cold and hot spots in the resulting dose distribution for pancreatic cancer patients (Dolde et al, 2018). Time-resolved imaging modalities like 4DCT and 4DMRI offer promising potential to take these uncertainties into account for image-guided radiotherapy of pancreatic cancer.

Intrafractional pancreas motion has been investigated based on 4DCT (Huguet et al, 2015, Hallman et al, 2012) or static CT in inhalation and exhalation state (Gwynne et al, 2009). Using repeated 4DCT (Shiinoki et al, 2011) and cone-beam CT (CBCT) scans (van der Horst et al, 2013), also interfractional differences in pancreas motion and position have been analyzed. However, the usage of these approaches is limited with respect to repeated imaging due to the high additional imaging doses from repeated 4DCT imaging and non-sufficient image quality of CBCT in the abdomen. Repeated imaging is, however, important for the analysis of pancreas motion due to large day-to-day variations (Minn et al, 2009). For this reason, MRI-based motion analysis approaches show great potential in the context of image guided radiotherapy, since they avoid additional imaging dose to the patients while offering a high image quality with high soft tissue contrast. Fast cine-MRI sequences were shown to be suitable for plane abdominal motion extraction (Bussel et al, 2003, Heerkens et al, 2014). 4DMRI, moreover, offers volumetric pancreas motion information (Stemkens et al, 2015, Stemkens et al, 2016). Due to the spatial motion information, 4DMRI shows a high potential to be used for the investigation of both inter- and intrafractional abdominal organ motion by means of repeated MRI measurements to investigate both setup reproducibility and day-to-day motion and deformation variations.

With respect to pancreatic motion reduction, a previous study (Heerkens et al, 2017) reported on reduced intrafractional pancreas motion amplitudes in inferior-superior (IS) direction by using a foam-based abdominal corset, finding no impact on anterior-posterior (AP) motion amplitudes. They quantified the motion by means of two cine-MRI measurements for each subject on two different days: one day without corset, on another day with corset. Another study (Fontana et al, 2016) compared different positioning modes (vacuum cushion, thermoplastic mask, and compressor belt) with respect to pancreas motion by acquisition of one 4DMRI per subject and reported on patient-specific results, based on rigid center-of-mass motion analyses.

Acknowledging the results of these studies, we extended the parameter space in our pancreas motion study. First, as day-to-day motion variations frequently occur, we investigated immobilization-induced motion reduction and motion reproducibility as two separate aspects by acquisition of multiple 4DMRI images on different days for each subject. With this approach, we were able to quantify both intra- and interfractional pancreatic motion behaviours, while the previous studies only reported on intrafractional effects. Second, we investigated pancreatic deformations and the influence of immobilization devices on the resulting deformations. Organ deformation is a relevant parameter for radiotherapy purposes as it may change the resulting dose distributions.

2. Material and methods

2.1. Pre-study for 4DMRI image quality improvement

In order to obtain a sufficient high contrast of the pancreas to its adjacent organs for subsequent pancreas delineations on the 4D-MR images, a contrast optimization pre-study was performed to adjust the flip angle $\alpha$. The 4DMR data were acquired, using a T1-weighted gradient-recalled echo radial stack-of-stars sequence with golden angle spacing (Block et al, 2014). Starting point of the optimization was the Ernst-angle configuration (Ernst and Anderson, 1966) with a flip angle $\alpha = 6^\circ$ for the repetition time (TR) and echo time (TE) being 3.3 ms 1.5 ms respectively, where the pancreas shows the highest signal intensity. Next, the flip angle was adjusted to improve the contrast of the pancreas to its adjacent organs by maximizing the difference in signal intensities between pancreas, liver, spleen and kidney, using the signal equation of gradient echo sequences

$$ S \propto \frac{1 - e^{-TR/T1}}{1 - \cos \alpha \cdot e^{-TR/T1}} \cdot e^{-TE/T2^*} \cdot \sin \alpha $$

The signal intensity $S$ depends on the free parameters TR, TE and $\alpha$ and on the tissue-specific relaxation times T1 and T2*, the latter were taken from literature (de Bazelaire et al, 2004, Schwenzer et al, 2008, Grassedonio et al, 2015) for pancreas, liver, spleen and kidneys. With both, the Ernst-angle setting and the optimized contrast setting, 4DMRI measurements of 9 volunteers were acquired on a 1.5 T MR scanner.
(MAGNETOM Aera, Siemens Healthcare, Erlangen, Germany) to investigate the contrast improvements. The raw data were reconstructed with an iterative reconstruction algorithm with k-space-center-based self-gating (Rank et al 2017), which provides 20 overlapping breathing phases for each measurement. Finally, the pancreas and its adjacent organs were delineated and the intensity-based contrast between the organ delineations was derived. The resulting images were evaluated statistically and by means of a blind analysis with three physicians who judged the image quality.

2.2. Main Study design

For the main motion study, 150 4DMRI data sets in total were acquired for five healthy volunteers V1-V5 (4 male, 1 female, age 21-28) in 10 imaging sessions respectively. The parameters of the optimized 4DMRI parameter setting were used for the measurements (field of view = \(400 \times 400\) mm\(^2\), voxel size \(1.5 \times 1.5 \times 3\) mm\(^3\), spokes per partition = 2100, bandwidth = 610 Hz, \(TE = 1.5\) ms, \(TR = 3.3\) ms, \(\alpha = 12^\circ\)). Measurement time for one 4DMRI measurement was approximately 8 min.

The measurements were performed within 2–4 weeks for each subject, simulating regular 4DMRI sessions of patients undergoing fractionated radiotherapy. For each imaging session, consecutive 4DMRI measurement were performed in three different immobilization modes (see figure 1). The volunteer laid in supine position

- in a personalized vacuum bag, (in the following: VB), see section 2.3.1
- in a personalized vacuum bag while wearing a personalized abdominal corset, (in the following: AC), see section 2.3.2 and
- on a flat table top with a knee pillow (in the following: FTT), see section 2.3.3

2.3. Positioning

For all measurements, the volunteers’ arms were positioned behind the head on a WingSTEP\textsuperscript{TM} (ELEKTA, Stockholm, Sweden), the way pancreatic cancer patients are positioned at the HIT (Heidelberg Ion-Beam Therapy Center) facility during proton therapy treatments. To ensure a reproducible setup, both the WingSTEP and the vacuum bag were mounted to a wooden fixation table top with indexing pins and indexing bars, see figure 1. The anterior MR body coil was directly placed on the volunteer, its position was adjusted for each subject individually and

![Figure 1. Setup at the MR scanner: A WingSTEP is mounted on a wooden flat table top fixation board (a), which contains indexing pins for the fixation of a vacuum bag via indexing bars (b). The volunteer measurements were performed in three different positioning modes: with a vacuum bag (b), with both vacuum bag and abdominal corset (c) and on the flat table top with a knee pillow (d).](image)
reproducibly repositioned for every measurement using the positioning laser of the MR scanner.

2.3.1. Vacuum bag
For each volunteer, a personalized vacuum bag was fitted. Such vacuum bags are regularly used for radiotherapy setup in our institution to facilitate a reproducible positioning of the patient. Two plexiglas indexing bars were mounted to the cranial and caudal part of the bag for latching the bag to indexing pins on the flat table top fixation board.

2.3.2. Abdominal corset
In cooperation with the Orthopedic Hospital Heidelberg, rigid MR-compatible abdominal corsets (Basko Healthcare, Boston Overlap Brace), consisting of homogeneous polyethylen were fitted on both size and body shape of the volunteers. The corsets were framed around the abdominal region of the volunteers from the ribs to the hip and were closed anteriorly with four hook-and-pile fasteners, which were labelled to ensure a reproducible corset pressure for each measurement.

2.3.3. Flat table top fixation board
A flat table top fixation board was developed in-house to provide a flat rigid surface for the MR scanner table for radiotherapy compatibility. The board has pin holes on different positions to mount indexing bars of vacuum bags and a WingSTEP on it.

2.4. Image registration and extraction of motion
For all 4DMRI data sets of the main study, the end-exhale (EEX) breathing phase image was taken as a reference phase and registered to all 19 other breathing phases of the same measurement.

For image registration, we defined a workflow in AVID (analysis of variations in interfractional radiotherapy), a workflow automation software for handling large collections of patient data. MatchPoint (Floca 2010) was used as an image registration framework within AVID. Inside the framework, the plasmatch implementation of the demons algorithm (Thirion 1998) was used to perform the deformable image registrations (DIR).

The pancreas was manually segmented on the EEX and end-inhale (EIN) breathing phase of each measurement.

The motion for all voxels within the segmentation was extracted by applying the EEX segmentation as a binary mask to the respective deformation vector fields (DVF), obtained from image registration. The resulting motion-volume-histograms (MVH) were used for motion quantification purposes.

2.4.1. Data analysis
The 4DMRI data were analysed with respect to different aspects:

• In a motion reduction analysis, the impact of the different immobilization devices on the pancreas motion amplitudes was analyzed and quantified by comparing the mean motion amplitudes $\mu_i$ between $EIN$ and $EEX$ among the ten fractions were used as a surrogate of motion amplitude fluctuations (see section 3.2). For each volunteer, the average $\mu(\sigma)$ of the motion amplitudes among different fractions was calculated and the ratio between different positioning modes was used to quantify relative motion reductions.

• Day-to-day changes of pancreatic motion were investigated for all positioning devices. For this purpose, the standard deviations $\sigma(\mu_i)$ of the mean motion amplitudes between $EIN$ and $EEX$ among the ten fractions were used as a surrogate of motion amplitude fluctuations (see section 3.3). Small $\sigma(\mu_i)$, i.e. very similar motion amplitudes between different fractions, indicate a better reproducibility (higher precision) of motion amplitudes than large $\sigma(\mu_i)$. The ratio of two $\sigma(\mu_i)$ values, derived for different positioning modes, were used to quantify the relative improvements with respect to motion reproducibility. For each of the subjects, two data sets were available, which were acquired on the same day. These were used to investigate the motion reproducibility within a single day. These data sets were taken within 3 h.

• In line with the pancreas motion analysis, the pancreatic deformations were quantified using the standard deviations $\sigma_i$ of the underlying MVHs for all fractions $i$ between $EIN$ and $EEX$ (see section 3.4) as a deformation surrogate, as larger standard deviations indicate a broader voxel-wise motion distribution and thus larger deformations. For each subject, the average $\mu(\sigma)$ among different fractions was calculated and its ratio between different positioning modes was used to quantify relative deformations reductions.

• Reproducibility of pancreas deformation was characterized by the standard deviation of the distribution of MVH standard deviations $\sigma(\sigma_i)$ among the 10 fractions (see section 3.5). The ratios of two $\sigma(\sigma_i)$ values were used to quantify the relative improvements in deformation reproducibility.

• In a volunteers setup analysis, both, the Dice coefficient and the center of mass offset of the EEX pancreas segmentations between fraction 1 and fraction 2–10, were used to quantify the setup reproducibility for each volunteer (see section 3.6).

The schematic workflow is illustrated in figure 2, depicting the study design with 5 volunteers, 10 fractions and 3 positioning modes, the data processing with deformable image registrations and motion extraction, and the subsequent data analysis parts.
2.5. Registration quality assurance and robustness analysis

Registration quality was evaluated by calculating the Dice coefficients and maximum Hausdorff distances between the warped EEX segmentations, warped from EEX to EIN (called: EEX-to-EIN), and the delineated EIN segmentations, revealing the overlap between the particular segmentations and the maximum distance between the segmentations, respectively. In radiotherapy, Dice coefficients are recommended to be between 0.8–0.9 for appropriate deformable image registration quality (Brock et al 2017).

Additionally, to investigate volume conservation, the Jacobian determinants of the DVFs between EEX and EIN were calculated within the EEX delineation of the pancreas. Moreover, the difference of the mean signal intensities between the EIN images and the mapped EEX-to-EIN images (warped by the respective DVF) within the EIN pancreas delineations were calculated to investigate intensity conservation at voxel level. These two metrics provide additional information with respect to registration quality.

In order to evaluate the impact of registration uncertainties on the extracted motion quantities and the derived conclusions with respect to motion and deformation reduction, a robustness analysis was performed in the following way: from the distribution of maximum Hausdorff distances, the average maximum Hausdorff distance $D$ was calculated. This value $D$ was then used to artificially shift the EEX pancreas segmentations by $D$ mm in all spatial dimensions on the underlying EEX MR image, on which the delineation had been performed ($\pm D$ in IS, $\pm D$ in AP, $\pm D$ in LR direction). Next, the MVH, containing the motion amplitudes of all voxels inside these shifted segmentations (with their new coordinates after the shift), was extracted from the respective DVFs. These six worst-case assumptions are considered as an upper estimate of the registration uncertainties. Finally, all data analysis steps were repeated for these six worst-case scenarios to evaluate the robustness of the determined motion/deformation reductions and the reproducibility improvements, which are reported in the results section.

If the originally derived values were within the 1-sigma range of these worst-case scenarios (with overestimated registration uncertainties), we concluded that the intrinsic registration uncertainties do not have a pronounced impact on the conclusions, drawn from the study.

3. Results

3.1. Contrast optimization and image quality

The pre-study 4DMRI contrast optimization suggested an optimum flip angle of $\alpha = 10^\circ$–$12^\circ$ to achieve a high contrast of the pancreas to its adjacent organs. This was confirmed in 9 volunteer measurements, where this optimized settings showed higher contrast of the pancreas to its adjacent organs than the Ernst angle setting ($\alpha = 6^\circ$) and provided sufficient image quality for subsequent pancreas delineations. This was confirmed by a blind analysis with three physicians, who in 78%–89% out of 9 cases confirmed that the images with the optimized flip angle with $\alpha = 10^\circ$–$12^\circ$ showed a sufficient and superior contrast than the Ernst angle setting. The contrast optimization results as well as exemplary EEX and EIN phases of one 4DMRI data sets are illustrated in figure 3, in which additionally a 3D polygon model representations the pancreas are displayed.

3.2. Motion analysis

The MVHs with the motion distributions of all voxels within the pancreas segmentations were extracted from the DVFs for all volunteers and fractions for VB,
AC and FTT positioning modes. The 3D motion distributions were separated into inferior-superior (IS), anterior-posterior (AP) and left-right (LR) motion amplitudes between EIN and EEX and are illustrated in figure 4.

As a consequence of breathing motion, the largest motion amplitudes were observed in IS direction, followed by AP and LR. Both, subject-specific motion patterns as well as intra-subject differences are visible. V3 shows the largest motion amplitudes with maximum IS amplitudes >30 mm and AP amplitudes of up to 16 mm. LR motion is, as expected, comparably small with median amplitudes around 2 mm for most of the measurements and is therefore not considered substantial for the further analysis.

A pronounced motion reduction was observed in IS and AP direction for the measurements with AC, compared to measurements with VB or FTT. In IS, the range of mean pancreas motion amplitudes was reduced from 3.7–28.5/1.4–21.9 mm with FTT/VB to 0.7–9.3 mm for AC. This corresponds to an average motion reduction of 4.6 mm (48%) with AC (range for individual subjects: 12%–77%) with respect to FTT and 2.7 mm (34%, range: 3%–60%) with respect to VB. Additionally, the VB measurements showed slightly smaller IS motion amplitudes compared to FTT measurements with a mean motion reduction of 1.9 mm (20%, range 4%–43%).

In AP, a reduction from 0.5–9.0/0.3–6.8 mm with FTT/VB to 0.2–2.6 mm with AC was observed among the volunteers. In relative values, mean AP motion reductions of 69% (range 30%–86%) with FTT as a reference and 60% (range 12%–87%) with VB as a reference were calculated by means of AC. For V3, the mean motion amplitude was reduced by 2.2 mm (40%), due from FTT to VB. For the other subjects, only AP motion reductions < 1 mm were extracted comparing FTT and VB and thus considered negligible.

Figure 5 displays the distribution of mean motion amplitudes in IS and AP direction, containing all 10 fractions and showing the reduced motion amplitudes with abdominal corset and vacuum bag, most
pronounced visible for V3. Exemplary motion distributions within a breathing cycle are also depicted. The individual amplitude ranges of mean pancreas motion are listed in Table 1.

3.3. Day-to-day variations of pancreas motion

The standard deviations of mean IS motion amplitudes between different fractions were on average 62% lower for AC measurements (range 30%–170%) compared to FTT, implying an improved reproducibility of motion amplitudes by 62% by means of AC for all subjects. Similarly, a better reproducibility was also visible for AC compared to VB with a mean improvement of 77% among the 5 subjects. No difference was found between FTT and VB with respect to differences in motion precision.

In AP direction, the mean motion reproducibility was even more considerably improved for AC measurements, namely by 130% compared to FTT and by 128% compared to VB. No improvements were observed for VB compared to FTT. These results are illustrated in figure 6.

In summary, for all volunteers the reproducibility of pancreas motion amplitudes was strongly improved in IS and AP direction by using abdominal corsets.

The analysis of measurements which were acquired on the same day, also showed intra-daily motion variations. Between two FTT measurements on the same day, mean intra-daily IS motion variations of 27% (range 6%–44%) were derived among

Figure 4. Pancreas motion distribution for all voxels between end-inhale (EIN) and end-exhale (EEX) breathing phase for all 5 volunteers (V1-V5), 10 imaging sessions and three different positioning modes: vacuum bag (VB, green), abdominal corset (AC, red) and flat table top (FTT, blue). The top and bottom of each box display the 25th and 75th percentiles of the underlying data, the dashed whiskers include all voxels within a distance of 1.5 times the interquartile range from the bottom or top of a box.
the five subjects, while for VB and AC, slightly smaller variations of 24% (range 9%–58%) and 20% (range 9%–39%) were found.

### 3.4. Magnitude of pancreas deformation
The standard deviations \( \sigma_i \) of the MVHs for each individual fraction \( i \) are an indicator of the amount of pancreas deformation during a breathing cycle. The larger \( \sigma_i \), the more pronounced is the deformation. Pancreas deformations showed to be reduced when using abdominal corsets. This can already be visually concluded from figure 7, where standard deviations of the motion distribution are illustrated for volunteer V1. For V1, the deformation analysis shows small deformations in the AC measurements, \( (\sigma_i < 1.8 \text{ mm}) \) in contrast to the VB/FTT positioning \( (\sigma_i < 2.4/3.1 \text{ mm}) \). Generally, for 4 out of 5 volunteers, the pancreas deformation showed to be reduced on average by 50% (range 22%–71%) in the AC measurements compared to FTT and by 39% (range 17%–55%) compared to VB. For V2, no detectable changes were observed.

### 3.5. Day-to-day-variations of pancreas deformation
While the standard deviations \( \sigma_i \) of the motion distributions characterize the amount of pancreas deformation, the standard deviation of these values \( \sigma(\sigma_i) \) among the different fractions \( i \) of one volunteer indicate the reproducibility of pancreas deformation. The corset measurements showed the most reproducible pancreas deformations, followed by vacuum bag measurements.

In detail, the interfractional changes in pancreas deformation were on average reduced by 77% (range 3%–267%) with AC, compared to FTT and by 31% (range −23%–167%) compared to VB. Moreover, higher reproducible pancreas deformation was obtained for VB compared to FTT by 35% (12%–62%). The day-to-day deformation variations are illustrated in figure 7.

### 3.6. Volunteer setup analysis
The FTT setup showed the highest center of mass offsets of the pancreas segmentations, which on average showed to be reduced by 5.7/3.1 mm by means of a VB/AC setup. Similarly, the lowest Dice

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**Figure 5.** Distributions of mean pancreas motion amplitudes for all 5 volunteers and 3 positioning modes between end-inhale and end-exhale breathing phase in IS (a) and AP direction (b). Exemplary motion distributions for volunteer 1 in one specific fraction illustrate the time dependence of the motion amplitudes in IS (c) and AP direction (d) for all 20 breathing phases and reveal the reductions by means of AC.
of pancreas delineations among the different 4DMRI data sets, indicating sufficiently high Dice coefficients > 0.8 were present (mean: 0.86; range 0.82–0.90), fulfilling the criteria for image registration with respect to radiotherapy, where a Dice coefficient tolerance of 0.8–0.9 is recommended (Brock et al 2017). Exemplary EIN and EEX-to-EIN pancreas segmentations are illustrated in color-coded overlayed in figure 9 to visualize the registration output.

Additionally, mean Jacobian determinant values of 1.02 ± 0.05 were determined within the EEX pancreas delineations among the different 4DMRI data sets, indicating sufficient volume conservation. Comparisons of the mean intensity values between the EIN and the mapped EEX-to-EIN image yielded mean differences of 2.5 ± 7.5 MR intensity units within the pancreas delineations. The pancreas itself showed mean intensity values of 253 ± 23 intensity units.

To assess the relevance of the remaining registration uncertainties with respect the derived results on motion/deformation reductions and reproducibilities, a robustness analysis was performed, for which an average maximum Hausdorff distance of $D = 11.7$ mm was extracted from the initial and warped segmentations. The EEX pancreas segmentations were then shifted by 8 pixels (12 mm) in all spatial dimensions (± 8 pixels in IS/AP/LR direction, respectively) before the voxel-wise motion extractions and analyses were performed for these worst-case scenarios.

The original reduction or improvement values, reported in the results section, were evaluated with respect to the results of the robust analysis (RA). The results are listed in table 2.

All results were found to be consistent with the $1\sigma$-range of the robust analysis, except the deformation reproducibility of AC compared to VB, which showed larger improvements in the robust analysis than in the original results. It can be concluded, that the derived results with respect to pancreatic motion and deformation are robust against existing limitations and intrinsic uncertainties in segmentation and registration uncertainties in this study.

### Table 1. Range of mean pancreas motion amplitudes (min-max) in IS/AP/LR direction within 10 fractions for all volunteers.

| Volunteer | IS motion [mm] | AP motion [mm] | LR motion [mm] |
|-----------|----------------|----------------|---------------|
|           | VB  | AC  | FTT | VB  | AC  | FTT | VB  | AC  | FTT |
| V1        | 3.6–10.8 | 0.7–7.7 | 4.0–12.4 | 0.6–1.8 | 0.2–0.4 | 0.5–1.4 | 0.3–1.3 | 0.3–0.5 | 0.4–0.8 |
| V2        | 3.6–8.7 | 2.2–7.5 | 3.7–11.3 | 0.5–1.9 | 0.6–1.6 | 0.6–3.0 | 0.4–0.9 | 0.0–1.2 | 0.0–1.4 |
| V3        | 1.4–21.9 | 2.1–6.5 | 8.0–28.5 | 0.3–6.8 | 0.2–1.4 | 3.0–9.0 | 0.0–1.9 | 0.6–1.1 | 0.0–3.2 |
| V4        | 6.9–13.0 | 4.7–9.3 | 7.1–13.2 | 2.1–5.2 | 0.3–2.6 | 2.2–4.8 | 0.6–2.1 | 0.0–2.0 | 0.3–2.3 |
| V5        | 6.0–9.7 | 5.8–7.9 | 6.6–9.1 | 1.0–2.3 | 0.4–1.0 | 1.4–2.5 | 0.5–0.7 | 0.4–0.6 | 0.4–1.1 |

Section 3.7. Evaluation of image registration quality and robustness

Figure 9 shows the Dice coefficients between the pancreas segmentations in the end-inhale phase and the respective segmentations from the end-exhale phase, which were warped into the end-inhale phase by the respective deformation vector field. For all segmentations, sufficiently high Dice coefficients $> 0.8$ were present (mean: 0.86; range 0.82–0.90), fulfilling the criteria for image registration with respect to radiotherapy, where a Dice coefficient tolerance of 0.8–0.9 is recommended (Brock et al 2017). Exemplary EIN and EEX-to-EIN pancreas segmentations are illustrated in color-coded overlayed in figure 9 to visualize the registration output.

Additionally, mean Jacobian determinant values of $1.02 ± 0.05$ were determined within the EEX pancreas delineations among the different 4DMRI data sets, indicating sufficient volume conservation. Comparisons of the mean intensity values between the EIN and the mapped EEX-to-EIN image yielded mean differences of $2.5 ± 7.5$ MR intensity units within the pancreas delineations. The pancreas itself showed mean intensity values of $253 ± 23$ intensity units.

To assess the relevance of the remaining registration uncertainties with respect the derived results on motion/deformation reductions and reproducibilities, a robustness analysis was performed, for which an average maximum Hausdorff distance of $D = 11.7$ mm was extracted from the initial and warped segmentations. The EEX pancreas segmentations were then shifted by 8 pixels (12 mm) in all spatial dimensions (± 8 pixels in IS/AP/LR direction, respectively) before the voxel-wise motion extractions and analyses were performed for these worst-case scenarios.

The original reduction or improvement values, reported in the results section, were evaluated with respect to the results of the robust analysis (RA). The results are listed in table 2.

All results were found to be consistent with the $1\sigma$-range of the robust analysis, except the deformation reproducibility of AC compared to VB, which showed larger improvements in the robust analysis than in the original results. It can be concluded, that the derived results with respect to pancreatic motion and deformation are robust against existing limitations and intrinsic uncertainties in segmentation and registration uncertainties in this study.

Figure 6. The improved reproducibility of motion amplitudes is visible for measurements with abdominal corset AC in IS and AP direction. Moreover, the FTT setups shows the lowest reproducibility of pancreas deformations.

Figure 9. Shows the Dice coefficient volume conservation. Combinations of mean pancreas motion amplitudes (min-max) in IS/AP/LR direction within 10 fractions for all volunteers.
4. Discussion

This study shows a significant reduction of pancreas motion by using an abdominal polyethylene corset in IS and AP direction. A mean motion reduction of 4.6/2.7 mm (48%/34%) in IS and 1.9/1.3 mm (69%/60%) in AP direction is observed, comparing the measurements with corset to FTT/VB measurements. Especially the motion reduction in AP direction may have a huge impact on particle therapy for pancreatic cancer due to the risk of overshooting at the distal edge of the tumor. This for instance may lead to an unwanted dose deposition in the duodenum, which is in close vicinity to the pancreas head.

Previously, similar pancreatic tumor motion reduction by a polyurethan foam based corset of 4.1 mm on average in IS direction has been reported based on cine MRI measurement (Heerkens et al 2017), showing, however, no motion reduction in AP direction. The usage of different corsets in these two studies as well as patient-specific motion patterns may be a contributing factor, leading to the different reduction results especially in AP direction. Moreover, our study takes the entire pancreas motion into account, whereas Heerkens et al report on pancreatic tumor motion reduction, which are often situated in the pancreas head region and may show a reduced motion behavior compared to the pancreas tail (Fontana et al 2016).

Furthermore, while the measurements with and without corset in this previous study (Heerkens et al 2017) were performed on different days, in our case the measurements were performed on the same day (and repeated on different days respectively). Since we found pronounced day-to-day motion variations in our study, it may be beneficial to perform further investigations on the impact of abdominal corset on the same day. If the measurements with and without corset are performed on different days, it could be unclear how much impact the interfractional motion variations have on the reported motion reduction results.

We observe very patient-specific pancreas motion amplitudes and day-to-day motion variations. For instance for V5, IS motion amplitudes from 6.6–9.1 mm were observed for the FTT positioning mode.
with small day-to-day variations of the maximum motion amplitudes of only 2.5 mm. On the other hand, V3 shows IS amplitudes of 8.0–28.5 mm with large day-to-day variations up to 20.5 mm.

Other pancreatic motion investigations reported similar motion amplitudes of 6–34 mm (Heerkens et al 2014) and up to 20 mm (Feng et al 2009) motion in IS direction, determined from planar cine-MR images.

Depending on the motion amplitudes, the absolute motion reduction by the abdominal corset for volunteers with small pancreas motion amplitudes like V5 was rather small (reduction of 0.8–1.2 mm) compared to large motion volunteers like V3 (reduction of 14.2–22.0 mm). The advantages of using abdominal corsets may therefore be very patients-specific.

The observed day-to-day variations indicate the need for regular 4D imaging and online imaging during treatment. This is in agreement with results from a previous study (Minn et al 2009), which compared centroid pancreatic tumor motion from 4DCT scans to online motion observation by a respiratory tracking software. They found no correlation between the two results and concluded that a single 4DCT scan cannot predict the pancreatic tumor motion during treatment. However, by using abdominal corsets, the day-to-day variations could be strongly reduced by 62%/77% in IS direction and 130%/128% in AP direction, compared to FTT or VB measurements. Ensuring more reproducible pancreas motion may have advantages for treating patients with particle therapy, where time-resolved online imaging is still under development. More reproducible motion patterns may, for instance, be used for more accurate motion predictions to be included in 4D treatment planning for those patients.

To the best knowledge of the authors, pancreatic deformation during respiration has not been quantitatively investigated in literature yet. The proposed deformation surrogate, the standard deviation of the underlying MVH, showed to be a suitable quantity in

Figure 8. Differences in pancreas center of mass (a) and Dice overlap of the pancreas (b) for different fractions, comparing the end-exhale segmentations of the pancreas for fractions 2–10 to fraction 1.

Figure 9. Quality assurance of the image registrations. (a) The Dice coefficients between the EIN and the warped EEX-to-EIN pancreas segmentation for all volunteers (V1-V5) are within the recommended tolerances of 0.8–0.9. (b) Four exemplary 3D representations of overlayed EIN (green) and EEX-to-EIN (purple) pancreas segmentations. While the dull areas show a good agreement, the bright green and purple regions depict the non-overlapping parts of the delineations.
this study to quantify deformation reductions by abdominal corsets.

The proposed method of motion and deformation quantification holds intrinsic uncertainties, originating from deformable image registration, shown for instance by the Dice coefficients. However, as this study aims to determine suitable patient positioning modes in radiation therapy, we refer to the recommendations, defined for image registrations in the scope of radiation therapy, which state Dice coefficients of 0.8–0.9 to be sufficient (Brock et al 2017). Our findings with Dice coefficients > 0.81 are in agreement with these recommendations, as well as with abdominal contour propagations reported from other groups, who reported Dice coefficients of 0.73–0.88 (Liu et al 2014, Woerner et al 2018, Latifi et al 2018).

Moreover, performing a robustness analysis by means of shifting the pancreas segmentation by the calculated averaged maximum Hausdorff distance, enabled us to directly translate registration uncertainties into their impact on the statistical motion analysis, performed in this study. This robust worst-case analysis enabled us to investigate the influence of registration uncertainties on the performed motion and deformation analysis, and showed the results to be robust towards the registrations uncertainties.

We used the Demons algorithm for deformable image registration. The algorithm assumes that intensity values are preserved in the images to be registered. This requirement is fulfilled in this study, as the 4DMRI data were reconstructed by means of an iterative reconstruction algorithm (Rank et al 2017), in which every k-space line of the MR-measurement is used to provide image information for every resulting breathing phase of the resulting time-resolved 4DMRI data set. This is expected to result in comparable intensity values. We confirmed the assumption of preserved intensity values visually and by comparing the mean intensity values within the pancreas delineation from EIN and EEX, which showed negligible differences (mean differences < 2 MR signal intensity units).

4DMR imaging has shown to be a viable tool to observe and account for the resulting inter- and intra-fractional uncertainties. By means of the performed contrast optimization, we obtained 4DMR images in high quality, which facilitated the pancreas delineations.

Reproducibility of patient setup is very important in conventional radiotherapy without online-adaptation. Interfractional pancreatic position variations have previously been evaluated based on repeated cone beam CT (CBCT) scans for pancreatic cancer patients by comparing the displacements of intratumoral implanted markers (van der Horst et al 2013). They observed a center of mass displacement of the markers from 1.0–25.6 mm (mean 9.4 ± 4.8 mm) with values similar to our observations with 2.0–4.8 mm center of mass displacements of the entire pancreas (mean 10.6 ± 4.2 mm). We further observe an advantage of using vacuum bags for a higher reproducible setup, if no online correction is performed, yielding a reduced center of mass displacement and higher Dice coefficients.

A further important clinical aspect with respect to motion reproducibility is surely the time between the last meal of the subject and the measurement. However, in this study, the timing of the measurements was
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pancreatic motion reduction was observed in IS (Naumann et al 2013), which may vary by 20% within a single day and may show patient-specific measurements. We observed highly variable and volumetric organ motion extraction by repeated fractions, coming along with additional uncertainties or the need of re-planning. Moreover, it needs to be considered, that this study was performed with healthy and young volunteers who are a different subject cohort than it is usually the case for pancreatic cancer patients, and the required corporal fitness to tolerate abdominal compression may not be given for all patients.

5. Conclusion

In this study, 4DMRI shows its high potential for volumetric organ motion extraction by repeated measurements. We observed highly variable and patient-specific pancreas motion amplitudes, which may vary by 20% within a single day and may show larger fluctuations within different days. Pronounced pancreatic motion reduction was observed in IS (48%) and AP direction (69%), compared to measurements without immobilization. Moreover, pancreatic deformation reductions by 30%–40% were observed when using abdominal corsets while at the same time, the day-to-day variations of motion and deformation were mitigated, compared to flat table top and vacuum bag measurements. With respect to patient setup, vacuum bags showed to be superior to purely flat table top setups. Concerning radiotherapy treatments, where small motion and deformation amplitudes are desired with small day-to-day motion variations, the results from this volunteer study indicate, that the consideration of abdominal corsets is useful for certain patients.

Ethics approval and consent for publication
Volunteer data were acquired within a study protocol, which was approved by the ethics committee of the medical faculty of Heidelberg, votum number S-159/2017. All volunteers have given written informed consent for the utilization and publication of anonymized imaging data for research purposes.

Disclosure statement
By now, FM is an employee at Siemens Healthcare GmbH. No potential conflict of interest was reported by the other authors.

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