Comparing the effectiveness and efficiency of various gating approaches for PBS proton therapy of pancreatic cancer using 4D-MRI datasets

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Abstract
Abdominal organ motion may lead to considerable uncertainties in pencil-beam scanning (PBS) proton therapy of pancreatic cancer. Beam gating, where irradiation only occurs in certain breathing phases in which the gating conditions are fulfilled, may be an option to reduce the interplay effect between tumor motion and the scanning beam. This study aims to, first, determine suitable gating windows with respect to effectiveness (low interplay effect) and efficiency (high duty cycles). Second, it investigates whether beam gating allows for a better mitigation of the interplay effect along the treatment course than free-breathing irradiations.

Based on synthetic 4D-CTs, generated by warping 3D-CTs with vector fields extracted from time-resolved magnetic resonance imaging (4D-MRI) for 8 pancreatic cancer patients, 4D dose calculations (4DDC) were performed to analyze the duty cycle and homogeneity index $HI = d_{5}/d_{95}$ for four different gating scenarios. These were based on either fixed threshold values of CTV (clinical target volume) mean or maximum motion amplitudes (5 mm), relative CTV motion amplitudes (30%) or CTV overlap criteria (95%), respectively. 4DDC for 28-fractions treatment courses were performed with fixed and variable initial breathing phases to investigate the fractionation-induced mitigation of the interplay effect.

Gating criteria, based on patient-specific relative 30% CTV motion amplitudes, showed the significantly best HI values with sufficient duty cycles, in contrast to inferior results by either fixed gating thresholds or overlap criteria. For gated treatments with 28 fractions, less fractionation-induced mitigation of the interplay effect was observed for gating criteria with gating windows $\geq 30\%$, compared to free-breathing treatments. The gating effectiveness for multiple fractions was improved by allowing a variable initial breathing phase.

Gating with relative amplitude thresholds are effective for proton therapy of pancreatic cancer. By combining beam gating with variable initial breathing phases, a pronounced mitigation of the interplay effect by fractionation can be achieved.
1. Introduction

Particle therapy has been shown to be a viable radiation therapy option for pancreatic cancer patients, as it makes use of the high spatial accuracy of dose delivery by the Bragg-peak of particle beams (Terashima et al 2012, Shinoto et al 2013, Hong et al 2014). This enables a superior sparing of adjacent organs at risk (OAR) compared to conventional photon therapy. However, in the presence of respiratory motion, pencil beam scanning (PBS) particle therapy of abdominal tumors may easily lead to an interplay effect between the scanning beam and the tumor and organ motion (Phillips et al 1992, Bert et al 2008, Seco et al 2009, Knopf et al 2011). For pancreatic cancer treatment, this may cause pronounced CTV underdosage and dose heterogeneity inside the tumor volume (Batista et al 2018, Dolde et al 2018).

Moreover, the interplay effect in particle therapy has been shown to be directly correlated to the underlying target motion amplitudes (Dowell et al 2013, Dolde et al 2019b), which indicates that by reducing the motion amplitudes, the interplay effect could potentially be mitigated (Engelsman et al 2013). Such a motion reduction can be achieved by abdominal compressions or corsets (Heerkens et al 2017, Dolde et al 2019a). Although corset-based studies revealed a significant reduction of pancreatic motion, such an approach may not be eligible for all cases, depending on patient fitness and comfort. Alternatively, it is possible to restrict the effective target motion during irradiation by applying beam gating (Minohara et al 2000, Lu et al 2007, Mori et al 2010, Bert et al 2011, Zhang et al 2015, 2017), where the irradiation only happens if a certain gating criterion is fulfilled (such as if a certain breathing phase is reached).

Previous studies have shown that gating approaches in particle therapy can be remarkably improved by combining with rescanning techniques (Mori et al 2014, Zhang et al 2018) or by assigning beam spots to specific motion phases, during the treatment planning process (Graeff et al 2014). Both methods were shown to be able to further smears out the residual hot and cold spots that occur in standard gating scenarios. With respect to pancreatic cancer treatments, Mori et al performed a comparison of gated and ungated carbon ion beam treatments based on single 4D-CT images with 30% duty cycles around the end-exhalation phase (Mori et al 2010). They generally found small dosimetric differences between both treatment strategies, but a reduction of the excessive dose to normal tissue in the gated cases. Miki et al used the same gating criterion to investigate the dosimetric impacts using 4DCT-based field-specific target volume and OAR delineations (Miki et al 2016). They reported on sufficient CTV (clinical target volume) coverage and dose reduction to the OARs by means of a field-specific approach. However, neither of the studies compared different gating windows, nor considered day-to-day tumor motion variability as no repeated 4D images were available of the patients.

In this study, we first aim to determine suitable gating windows for PBS proton therapy of pancreatic cancer by a systematic comparison of different image-based gating scenarios with fixed gating thresholds, which were determined by mean/maximum CTV motion amplitudes, relative CTV motion amplitudes and CTV overlap criteria. All these criteria are determined based on 4D-MRI data sets, acquired for eight pancreatic cancer patients, with respect to prospective MR-guided proton therapy, where such real-time images could potentially be acquired and utilized during irradiation.

Second, in order to investigate the mitigation of the interplay effect along a gated treatment course, we acquired repeated 4D-MRI data sets of patients on different days and utilized them to include day-to-day motion variations in the subsequent 4D dose calculations for the fractionated gated treatments. This 4D-MRI-based approach enabled us to take into account variable patient-specific tumor motion information without exposing patients to any additional ionizing radiation for daily imaging purposes. Furthermore it allowed to investigate, whether for gated proton treatments a better mitigation of the interplay effect along the treatment course can be achieved compared to free-breathing irradiations.

2. Material and methods

2.1. Patient cohort and available image data

Eight pancreatic cancer patients (P1–P8) were enrolled in this study, for whom up to 6 repeated 4D-MRI scans were acquired during their fractionated treatments at the Heidelberg Ion-Beam Therapy Center (HIT). Moreover, a 3D treatment planning CT and a 4D-CT were acquired in the planning phase for each patient. On the planning CT, the target volumes (the clinical (CTV), internal (ITV) and planning (PTV) target volume), and organs at risk (OAR) were delineated by a radiation oncologist. The ITV was derived from the union of CTV and OARs. The PTV was considered.

Furthermore it allowed to investigate, whether for gated proton treatments a better mitigation of the interplay effect along the treatment course can be achieved compared to free-breathing irradiations.
provides 20 overlapping breathing phases. Deformation vector fields (DVFs) between the end-exhale breathing phase MR image (EEX) and all images from other breathing phases were calculated by deformable image registration (DIR) using the open-source software plastimatch and the demons algorithm (Thirion et al 1998). The obtained DVFs were utilized to warp the treatment planning CT of the respective patient to obtain various synthetic 4D-CTs for 4D treatment planning purposes. From each acquired 4D-MRI, one synthetic 4D-CT was derived. The idea of warping a static planning CT by means of 4D-MRI deformation vector fields was first suggested and demonstrated by Boye et al (2013) for liver patients and has recently been shown to be feasible for pancreatic cancer patients (Dolde et al 2018).

In addition to 4D-MRI, single-slice coronal cine-MRI measurements with 100 frames and a time resolution of \( \approx 4 \text{ frames s}^{-1} \) were acquired for each patient before each 4D-MRI measurements. The diaphragm position in cranio-caudal orientation was extracted from each of the frames and a mean length of breathing cycles was determined for each measurement. The calculated breathing cycles were later utilized as input for the subsequent 4D dose calculations. An overview on the available image data is listed in table 1.

| Pat | CTV volume (cm\(^3\)) | Mean CTV amp. (mm) | Max CTV amp. (mm) | Breathing cycle (s) | # 4D-MRI | \( T (F_0) \) (s) | \( T (F_1) \) (s) |
|-----|-----------------------|--------------------|-------------------|--------------------|----------|----------------|----------------|
| 1   | 51.9                  | 4–5                | 6–10              | 4.8–7.1            | 2        | 22.5           | 28.6           |
| 2   | 33.1                  | 2–3                | 3–11              | 2.8–3.7            | 6        | 17.0           | 16.5           |
| 3   | 95.1                  | 5–8                | 11–15             | 6.7–9.7            | 5        | 34.5           | 35.0           |
| 4   | 87.7                  | 2–3                | 6–8               | 3.7–5.9            | 2        | 30.4           | 31.3           |
| 5   | 194.8                 | 2                  | 3                 | 3.7                | 1        | 49.2           | 47.3           |
| 6   | 115.1                 | 2                  | 5                 | 5.6                | 1        | 41.9           | 43.2           |
| 7   | 112.0                 | 3                  | 4.5               | 10                 | 1        | 39.3           | 38.7           |
| 8   | 46.0                  | 3–4                | 5–6               | 2.9–3.7            | 2        | 22.5           | 22.7           |

2.2. Extraction of CTV motion and registration QA

The CTV motion amplitudes between different breathing phases were extracted for all voxels within the CTV by masking the DVFs with the CTV delineation from the treatment planning CT. The resulting motion distributions of all voxels within the CTV allowed a 3D extraction of CTV motion. In particular, the maximum CTV motion amplitude occur in the end-inhale phase, when using the end-exhale phase as a reference. Both mean and maximum motion amplitudes were determined from the motion distributions for all breathing phases. These were utilized later to define gating scenarios G1–G3, see section 2.3. On top of that, the EEX CTV delineation was propagated to all other breathing phases by means of the respective extracted DVFs. The overlap between CTV delineations in different breathing phases allowed the definition of gating scenario G4.

Jacobian determinants were calculated on the DVFs between EEX and the end-inhale breathing phase MR image (EIN) for the liver, kidneys and bowel to evaluate the registration quality with respect to volume conservation.

2.3. Definition of gating scenarios

For this study, four different image-based gating scenarios (G1–G4) have been defined, which are described as follows:

- G1: Beam on, if the mean CTV motion amplitude, relative to the end-exhale breathing phase, is \( < 5 \text{ mm} \).
- G2: Beam on, if the maximum CTV motion amplitude, relative to the end-exhale breathing phase, is \( < 5 \text{ mm} \).
- G3: Beam on, if the mean CTV motion amplitude relative to the end-exhale breathing phase is \( < 30\% \) of the mean CTV motion amplitude in the end-inhale breathing phase.
- G4: Beam on, if the overlap between the CTV delineation in the current breathing phase and the CTV delineation in the end-exhale breathing phase is \( > 95\% \).

The different gating scenarios are illustrated in figure 1 for one example patient and motion pattern, extracted from a 4D-MRI data set.

2.4. Evaluation of the gating efficiency and effectiveness

The efficiency of the gating scenarios G1–G4 was determined by calculation of the duty cycle (dc) that yields the time percentage during which the beam is turned on during the treatment, see figure 2. Large duty cycles lead to fast treatment times.
The gating effectiveness was evaluated by the magnitude of interplay effect in the CTV in a single fraction, determined by the dose homogeneity index $HI = d_{5}/d_{95}$. The quantities $d_5$ and $d_{95}$ describe the dose that 5% and 95% of the CTV volume receive, respectively. These dose quantities were determined based on 4D dose calculations (4DDC). In detail, for all patients, 3D single field uniform dose (SFUD) plans for pencil-beam scanning proton therapy were calculated on the treatment planning CT with two oblique posterior fields ($F_0/F_1$), using the PSI ray-casting dose calculation algorithm (Boye et al 2013, Zhang et al 2014) with a prescribed dose of 1.8 Gy (RBE) per fraction on the PTV. For a subsequent 4DDC, the time-stamps of each pencil-beam were estimated by considering the machine dynamics of PSI Gantry2 (Zhang et al 2015). Consecutively, taking into account the beam time stamps, the generated synthetic 4D-CTs, as well as the underlying DVFs, 4DDCs were performed to analyze the motion-induced impact on the resulting dose distributions. For patients with multiple available 4D-MRI data sets (and therefore multiple generated synthetic 4D-CTs) with different underlying motion patterns, HI and dc were separately calculated for each synthetic 4D-CT and then averaged.

The duty cycles (dc) and HI-values for gating scenarios G1–G4 were pairwise statistically tested for significance by multiple one-sided Wilcoxon Rank–Sum tests with a confidence level of 95%. The multiplicity of tests ($\alpha = 5\%$ to $\alpha/n = 0.42\%$).

2.5. Mitigation of the interplay effect by fractionation
In free-breathing proton irradiations, previous studies have shown that the interplay effect may be efficiently mitigated by fractionation alone, since variations in motion patterns and initial breathing phases occur at each fraction that redistribute the motion-induced hot and cold spots in the CTV (Dolde et al 2018, 2019b). However, it is unclear whether this conclusion also holds true for gated treatments with fixed gating threshold.

To analyze this fractionation-induced mitigation of the interplay effect, the 4D data sets of P2 and P3, for whom the largest number of 4D-MRI data sets were available (5 and 6, respectively), were utilized for a 4DDC-based interplay mitigation study in the following way:

Gating windows with residual motion amplitudes of 10%–90% (in steps of 10%) of the maximum CTV motion amplitudes in the end-inhale breathing phase were defined for P2 and P3, then 4DDCs were applied for simulating entire treatment courses with 28 fractions in order to determine the dependency of the interplay mitigation on the size of the gating window. For each fraction, the respective underlying motion pattern was randomly selected from the available patient-specific 4D data to simulate day-to-day motion variations. For each patient, the entire simulated treatment course was repeated 20 times with differently randomly sampled underlying motion patterns.

In these simulations, the irradiation start was triggered by the respective gating signal. In an consecutive 4D analysis, this trigger condition was relaxed to allow variable initial breathing starting phases for each treatment fraction. Thus, the delivery of the first beam was assumed to be delivered at an arbitrary time within the first open gating window.

The effectiveness of the mitigation of the interplay effect was quantified by HI, and was put in relation with the corresponding duty cycles.

3. Results

3.1. CTV motion amplitudes and irradiation times
Mean CTV motion amplitudes among the voxels within the CTV from 2–8 mm were observed for this patient cohort with maximum amplitudes of up to 15 mm. Breathing cycles varied between 2.9–10s. Irradiation time per field
(ROI/F1) was in a range of 16.5–49.2 s for free-breathing irradiation, depending on the tumor volumes. The details are listed in table 1. Mean Jacobian determinants of 1.00 ± 0.04 were calculated for the liver, kidneys and bowel. Exemplary representations of the acquired 4D-MR images and deformation vector fields are illustrated in figure 3.

### 3.2. Evaluation of the gating efficiency and effectiveness

Gating scenario G3 (relative 30% motion amplitude threshold) showed the significantly lowest duty cycles (median duty cycle of 50%) from all scenarios G1–G4, followed by G2 and G4, see figure 4. G1 (5 mm mean motion amplitude threshold) was found to be unsuitable for this patient cohort, as mean CTV motion amplitudes >5 mm were only observed for one patient (P3), which lead to 100% duty cycles (i.e. no beam gating) for 7 out of 8 patients. G4 lead to larger duty cycles than G2.

In contrary, with respect to gating effectiveness, G3 showed the significantly best results with the lowest HI values, while G1 lead to the highest dose heterogeneity in the CTV. The differences, found between G1, G2 and G4 for both duty cycles and HI, were not significant.

### 3.3. Mitigation of the interplay effect by fractionation

Figure 5 shows the evolution of the interplay effect along the treatment course for gating scenarios with different residual motion amplitudes for P2 and P3, as well as for free breathing irradiations. The latter yields an effective fractionation-induced mitigation of the interplay effect. In contrary, the mitigation of the interplay effect by fractionation was limited for all considered gating scenarios along the entire treatment course with 28 fractions.

In free-breathing treatments, the initial breathing phase likely varies from fraction to fraction which leads to a statistical wash-out of the hot and cold spots, caused by the interplay effect. However, in gating scenarios, where the start of the irradiation is triggered by a fixed threshold criterion, the first pencil beam would always be delivered in the same breathing phase. Therefore, fractionation-induced mitigation of the interplay effect in gated scenarios may only occur due to day-to-day motion variations, which results in a much lower mitigation of the interplay effect.

For P3, considering a 50% gating window, already after 7 fractions the free-breathing treatments revealed a lower HI value than the gated ones. After 20 fractions, non-gated scenarios showed a lower HI value than 40% gating windows and after the entire treatment course with 28 fractions, the HI values were the same for non-gated scenarios and 30% gating windows. For P2, the interplay effect was generally lower due to smaller CTV motion amplitudes, but similar mitigation behaviors of gated and non-gated scenarios were observed. All in all, the results indicate that, from a statistical point of view, gating is especially effective for treatments with small number of fractions. In such cases, less residual interplay effect is present for gated than for non-gated treatments. For large numbers of fractions, free-breathing treatments lead to a superior mitigation of the interplay effect. For gating windows with residual motion amplitudes <30%, however, gated scenarios showed lower interplay effects for any number of fractions.

Naturally, tiny gating windows (e.g. 10%) would lead to almost no residual interplay effect. However, to avoid elongated treatment times, the general trade-off between efficiency and effectiveness of the gating window needs to be considered, which is illustrated in figure 6.
The combination of, first, the better (lower) HI values in a single fraction by the application of beam gating, and second, the pronounced fractionation-induced mitigation of the interplay effect by variation of initial breathing phases in free-breathing irradiations, showed to further improve the dose homogeneity for gated treatments. While the overall duty cycles do not change by allowing a random time point within the first gating window for delivery of the first beam, the resulting HI-values along the treatment course showed to improve by allowing variable initial breathing phases in gated treatments. Figure 7 illustrates the results for gated treatments with fixed and variable initial breathing phases for a gating window that allows 50% residual CTV motion amplitudes. By such variable breathing initial breathing phases, a further resulting mitigation of the interplay effect by fractionation could be achieved and lower residual interplay effects than in free-breathing deliveries was present for any number of fractions.

4. Discussion

Intra-abdominal organ motion leads to a substantial interplay effect in proton therapy of pancreatic cancer. Our results show that the application of beam gating with gating windows based on relative 30% motion amplitudes (G3), allow an effective mitigation of the interplay effect with an acceptable median duty cycle of 50%. In this study, such individual gating criteria with relative motion amplitudes showed to be superior to fixed gating-thresholds or image-based 95% CTV overlap criteria. Naturally, a high effectiveness comes along with lower duty cycles and a compromise between both needs to be determined in clinical workflows.

In this study, gated irradiations showed their highest potential for small numbers of fractions, e.g. in hypofractionated treatments, where no sufficient fractionation-induced mitigation of the interplay effect occurs. With respect to fractionation-induced mitigation of the interplay effect, our results show that from a statistical point of view, the residual interplay effect after a large number of treatment fractions may be smaller in free-breathing treatments than for gated treatments with fixed initial breathing phase, due to variable initial breathing phases in...
free-breathing scenarios. However, when combining variable initial breathing phases with gating constraints, the most effective interplay mitigation was observed along a 28-fractions treatment course.

Our results indicate, that in the underlying patient cohort, the most dominant factor in interplay mitigation is the variability of initial breathing phases in multi-fraction treatments. Nevertheless, although free-breathing treatments show a more pronounced interplay mitigation, for each individual treatment fraction the magnitudes of motion-induced hot and cold spots are still smaller in gated treatments. Therefore, the impact of reduced over-/underdosage in individual fractions by means of gating criteria should be evaluated separately from a biological point of view with focus on dose response after each fraction. On top of that, we would like to point out, that variations of beam delivery parameters, such as the energy layer switching time, may lead to a higher
mitigation effect during fractionation, even for fixed threshold gating treatments, than it was the case in the ideal dynamic beam delivery model that was assumed in this study. A previous study, however, found that the impact of motion variations, which are also considered in this study, are larger than the impact of differences in the delivery timeline (Krieger et al. 2018).

All gating scenarios, investigated in this paper, are based on image-based gating criteria, assuming 3D time-resolved real-time MR imaging during irradiation treatments. We are aware that this is not yet generally available or clinically implemented, neither in conventional photon, nor in proton therapy. However, the introduction of hybrid MR-LINACs (Lagendijk et al. 2008, Fallone 2014, Keall et al. 2014, Mutic et al. 2014), combining photon irradiation with online MR imaging, is an important step in this direction and first studies have been performed to combine 4D-MRI with 2D cine MRI to obtain online volumetric motion information (Stemkens et al. 2016, Kontaxis et al. 2017). On MR-LINAC devices, gating scenarios like G4 (CTV overlap between different breathing phases) are already in use, where the beam is turned on if the contoured and tracked CTV is located within a predefined region, visualized on fast 2D cine-MRI (Fischer-Valuck et al. 2017). In their case, a 90% overlap criterion is used. However, our study indicates that such a criterion may not be appropriate for pancreatic cancer, as for most of the cases in this study, such a criterion would have been fulfilled in all breathing phases and no gating effect would occur. This study indicates, that gating criteria with >95% CTV overlap would have been necessary for the underlying patient cohort to achieve an effective motion mitigation.

Besides, as pancreatic tumors often show a non-negligible anterior–posterior motion in addition to the major inferior–superior motion, pure 2D image-based gating scenarios may not be sufficient. While 4D-MRI is still too computationally intensive to allow online imaging nowadays, promising deep-learning based methods are being developed to reduce both imaging and reconstruction time for k-space sampled MR images with high image quality (Han et al. 2018). Alternatively, interleaved orthogonal cine-acquisitions may be used to obtain volumetric tumor position information for image-based gating scenarios (Seregni et al. 2016). With respect to MR-guided proton therapy, first feasibility studies are currently ongoing (Schellhammer et al. 2018) to investigate online MR imaging during proton irradiation. The combination of these recent results may enable volumetric time-resolved MR-based online imaging for proton therapy in the future.

This study was not intended to investigate the practicability or reliability of different gating surrogates. It rather focused on the general gating efficiency and effectiveness, and on the influence of day-to-day motion variations with respect to a mitigation of the interplay effect along a gated treatment course. The choice of the physical gating surrogate (internal, external) and its correlation to the actual tumor motion is subject to further investigations. In particular, external gating surrogates, like pressure belts (e.g. Batista et al. 2018) or surface imaging (Zhang et al. 2017) are currently used in clinics to provide surrogate breathing curve signals and allow the definition of gating scenarios with threshold values based on such surrogate data. Even if the positions of external surrogates and the CTV positions do not perfectly correlate, still, different width of gating windows may be defined based on surrogate signals, which will influence the residual motion and the consecutive amount of interplay effect, as demonstrated in this study.
Although the 4D-MRI based method used in this study can take tumor motion variations into account, the procedure does not fully account for interfractional variations in patient geometry, like weight loss of patients, which often happens for pancreatic cancer patients (Naumann et al 2013). Moreover, we did not consider baseline shifts in this gating study but assume regular motion patterns with a fixed baseline. In real patient treatments, baseline shifts may reduce the duty cycles and may show the need for compensation by dynamic gating windows (Pepin et al 2011). Additionally, we did not adapt the PTV margins according to the respec- tively chosen gating windows, but performed the 4DDC on the initially clinically delineated PTVs, which were delineated with respect to free-breathing irradiation. In prospective studies it would be interesting to investi- gate dosimetric impacts when considering gating-specific margins, determined for specific gating scenarios.

Additionally, this study only investigated motion-induced dosimetric impacts on the CTV, and did not consi- der impacts on OARs. In a previous study (Dolde et al 2019b), however, which investigated the interplay effect in free-breathing proton treatments of pancreatic cancer, we analyzed the dosimetric impact on OARs (liver, kid- nes, bowel, spinal cord) and found no significant differences between static 3D plans, and 4DDC scenarios after 1 and 28 fractions, respectively. Therefore, we would not expect pronounced dosimetric differences for the OARs in gated scenarios with reduced motion, compared to free-breathing scenarios.

Our study further contains intrinsic uncertainties due to the performed deformable image registrations. Registration errors translate into 4D dose calculations errors and may lead to dosimetric uncertainties of a few percent (Ribeiro et al 2018), which needs to be considered when interpreting 4D dose distributions. Therefore, the choice of suitable image registration algorithms is important. The Demons algorithm that was also utilized in this study has been determined to be suitable in a previous study (Ribeiro et al 2018). Moreover, the method of warping static CT images by 4D-MRI DVFs comes along with geometrical uncertainties, especially if the images were acquired on different days. In this study, Jacobian determinants were utilized as a measure of registration quality and showed sufficient values of $1.00 \pm 0.04$ inside the OAR delineations and confirmed volume conserva- tion of the registrations.

We are further aware that, based on the small patient cohort of 8 pancreatic cancer patients, enrolled in this study, it is not possible to generally conclude on the quantitative impact of gating on the interplay effect. In pro- spective studies, more patients with multiple 4D data sets should be included to increase the statistical power of the analysis.

Instead of gating approaches, other motion reduction techniques by abdominal corsets (Heerkens et al 2017, Dolde et al 2019a) could also be considered for pancreatic cancer treatments, possibly even in combination with beam gating. Alternatively, breath-hold irradiations could also be an adequate solution, where especially end-exhalation breath-holds showed very stable pancreas positions in healthy volunteers (Lens et al 2016). All in all, our study determined relative gating windows, based on 30% motion amplitudes, to lead to an effective mitigation of the motion-induced dosimetric heterogeneity in the CTV, while keeping the duty cycles at a tolerable level. Furthermore, we found that beam gating itself does not lead to an improved fractionation-induced mitigation of the interplay effect, compared to free-breathing treatments. However, when combined with variable initial breathing phases, gating is a promising strategy to effectively mitigate the interplay effect for PBS proton therapy of pancreatic cancer along the treatment course.

5. Conclusion

Abdominal organ motion leads to a pronounced interplay effect in PBS proton therapy of pancreatic cancer. This study determined beam gating with gating windows, based on relative 30% motion amplitudes, to be suitable for the investigated patient cohort, leading to an effective improvement of the dose homogeneity in the CTV. On the other hand, gating windows with fixed threshold amplitudes or image-based CTV overlap criteria yielded large duty cycles, but could not sufficiently reduce the motion-induced dosimetric impacts.

With respect to an effective mitigation of the residual interplay effect along the entire treatment course, the study suggests the use of variable initial breathing phases in gated treatments rather than purely fixed thresh- old-based gating windows that trigger the irradiation. Such an approach combines the gating advantages of low interplay effects in every single fraction by reduced residual tumor motion during irradiation with a further effective fractionation-induced mitigation of the interplay effect.

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Consent for publication

Written informed consent for proton/carbon treatment and repeated MR imaging for positioning control as an individual treatment approach as well as permission to publish treatment related data in an anonymized way was obtained from all patients.

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