Respiratory motion management for radiotherapy of pancreatic cancer patients
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Chapter 7

General discussion
Respiratory-induced pancreatic tumor motion during radiotherapy may lead to a reduction of the treatment efficacy, due to tumor miss and blurring of the dose. The quantification of the respiratory-induced pancreatic tumor motion, as well as different approaches to account for the respiratory-induced motion are presented in this thesis.

First, we showed that the respiratory-induced pancreatic tumor motion magnitudes measured on the single pre-treatment 4DCT scan were not representative for the daily tumor motion (chapter 2). So, the tumor motion used for treatment planning is often significantly different than the tumor motion during daily treatment.

Next, we investigated the applicability and potential dosimetric benefit of using mid-ventilation and a probabilistic treatment planning approach, compared with the use of an internal target volume (ITV) (chapter 3 and 4). Mid-ventilation proved to be superior compared with the use of an ITV in terms of dose to surrounding OARs, but probabilistic planning only showed a limited benefit. The extent of the dosimetric benefit strongly depended on the respiratory-induced motion magnitude, and both techniques still required the information obtained from the 4DCT. Also, both techniques would require the implementation of daily 4D-CBCTs when used in everyday practice.

We also investigated the application of breath-holding, which was assumed to eliminate the intrafractional tumor motion. Surprisingly, we observed considerable tumor motion during inhalation breath-holding and substantial variation in tumor position between consecutive inhalation breath-holds within a single fraction (chapter 5). Based on these results and the fact that some groups used exhalation breath-holds to achieve abdominal tumor stability, we investigated a possible optimization of the breath-holding procedures. We investigated the influence of lung volume during breath-holding on the organ motion during that breath-hold (chapter 6). We observed significantly smaller motion magnitudes during exhalation breath-holds and the motion was most pronounced at the start of breath-holding. In addition, we found that, because of the more pronounced tumor motion during this period, it may be beneficial to delay the irradiation of the patient by excluding the first 10 s of breath-holding. However, the inter-breath-hold position variation between consecutive breath-holds after these first 10 s should be determined and included in the safety margins when implemented in the clinic.

Respiratory motion management for other tumor sites

The work presented in this thesis focused on the pancreas as the main treatment site and all patients that were included were pancreatic cancer patients. However, other organs and anatomical structures undergo respiratory-induced motion as well, and the corresponding problems and solutions that are discussed in this thesis could also affect these organs.

Lung tumors almost always undergo respiratory-induced motion. The motion magnitude of lung tumors is highly dependent on the tumor location within the lung and whether the tumor is attached to other structures. A mean magnitude of 7 mm in the IS direction was observed when all tumors at different locations were combined [1]. Another study reported a mean motion magnitude of 12 mm in the IS direction for lung tumors located in the lower lobes of the lung and not attached
to any rigid structure [2]. These motion magnitudes are similar to what we observed for the pancreas and the techniques that can be used to account for the pancreatic tumor motion can also be used in lung.

To quantify the lung tumor motion, often a single pre-treatment 4DCT is acquired. Lung tumors are often clearly visible on CT and CBCT imaging, in contrast to pancreatic tumors, and image registration to determine tumor displacement can therefore be done simply based on tumor matching. Guckenberge et al. showed that a single 4DCT scan is sufficient to describe daily tumor motion for the majority of patients [3], but Sonke et al. showed that there can be substantial variation in the motion magnitude and they recommended to use daily respiratory correlated CBCT imaging [4]. Intrafractional motion of pancreatic tumors is not only determined by the respiratory-induced motion, but for example also by the gastrointestinal motion of nearby organs. Whether a patient has an empty or full stomach might also affect the mobility of a pancreatic tumor and this can result in a larger daily variation of the respiratory-induced motion magnitude compared with lung tumors. This is possibly one of the reasons that for pancreatic tumors, in contrast to lung tumors, we observed significant differences between the respiratory-induced pancreatic tumor motion on 4DCT and on daily CBCT.

It was shown that the ITV concept works well for lung tumors [5]. However, the dose to healthy tissue could be reduced further by an optimization of the respiratory motion management [6]. Because of the broader beam penumbra in lung [7,8], the safety margins can be reduced when the treatment plan is based on the tumor in its mean respiratory position. Combining daily 4D-CBCT imaging with the broad beam penumbra in lung led to the introduction of using the mid-ventilation (or mid-position) technique to reduce the PTV for lung tumors [9,10]. For lung tumors it has been shown, in a group of 297 patients, that mid-ventilation is a safe approach [11]. In chapter 3 we showed that the mid-ventilation concept also works well for pancreatic tumors. However, because of the difference between the beam penumbra in the lungs and in the abdomen, the reduction of the PTV when using mid-ventilation compared to using an ITV is smaller for pancreatic tumors.

The average respiratory-induced motion magnitude of the diaphragm has been investigated in a number of studies and was reported to be 8–26.4 mm [12–16]. As a result of the diaphragm motion, tumors in the upper-abdominal region undergo respiratory-induced motion (as shown for the pancreas in chapter 1). Liver tumors often have large respiratory-induced motion magnitudes. The mean respiratory-induced liver motion was reported to be 8–25 mm in the IS direction [13,15,17–21]. The kidneys are also affected by respiratory-induced motion, with reported motion magnitudes of 11–19 mm [15,18,19]. Respiratory-induced motion management techniques for the liver and kidneys are very similar to what is being used for the pancreas. However, the intrafractional motion of pancreatic tumors can be slightly different due to the close proximity to the duodenum. Each gas bubble that passes the duodenum can influence the position of the pancreas. Also, because the duodenum is an OAR, a sharp dose gradient around the pancreatic tumor is desired. So, good respiratory motion management is arguably more complex for the pancreas and focus should be on strategies to minimize this motion. These techniques should be (relatively) easy to implement so that
they can be used in the majority of the clinics. Examples of such strategies are abdominal compression and breath-hold [22,23].

**Reduction of intrafractional motion**

Using techniques such as mid-ventilation and probabilistic planning to account for the respiratory-induced pancreatic tumor motion, as described in chapter 3 and 4, do result in smaller PTVs. However, these techniques still have to account for the potentially large variations in the respiratory-induced motion magnitudes that are shown in chapter 2. Therefore, minimization of the respiratory-induced motion may be beneficial.

**Abdominal compression**

Abdominal compression can be used to reduce respiratory-induced organ or tumor motion. This is achieved by applying external pressure to the upper-abdominal region of the patient. This reduces the diaphragm motion and consequently the organ and tumor motion [24]. Abdominal compression has been shown to successfully reduce respiratory-induced liver motion [25,26] and it was also shown that the liver deformations while using abdominal compression were small for the majority of patients [22]. The respiratory-induced motion of lung tumors located in the lower lobe (i.e. lung tumors that experience the largest motion magnitude) can also be reduced by using abdominal compression and different levels of compression result in different levels of motion reduction [27]. This technique is widely used for stereotactic body radiotherapy (SBRT) [28] including SBRT of the pancreas [29].

This technique may be relatively easy to implement since it demands no additional training of the patient. However, the system still has to be purchased and commissioned, and using compression on a daily basis may increase the time that the patient is on the treatment table due to the daily set up of the system. Also, the system might not be MR-compatible, which in the current clinical practice, where the MRI is increasingly integrated in the radiotherapy workflow, can be undesirable.

**Breath-holding**

For multiple tumor sites, including in the upper-abdominal region, breath-holding has been used to reduce the intrafractional tumor motion. Breath-holding, both inhalation and exhalation, has been shown to be feasible for abdominal cancer patients [30–35]. The observed breath-holding durations in chapter 6 show that inhalation breath-holding is the most feasible for subjects compared with exhalation. In our patient study we found that breath-holding durations of 30 s should not be a problem for the average patient, but we also showed that inhalation breath-holding resulted in large geometric uncertainties. Several studies that have applied breath-holding for pancreatic cancer patients (either at inhalation or exhalation) did not investigate tumor motion during breath-holding [31,34,35]. This is surprising since organ motion during breath-holding was already observed in healthy volunteers for almost two decades ago [36,37]. Also, a phase 2 study showed that using SBRT with respiratory-induced motion management including breath-holding and very small margins of 2–3 mm resulted in minimal toxicity and even a possible increase in overall survival of pancreatic cancer patients [38].
This is striking, because based on the results from chapter 5 and 6 (example shown in Fig. 7.1) these margins would most likely be too small. Based on the geometric uncertainties during breath-holding described in this thesis a PTV margin of at least 5–7 mm would be necessary to account for the tumor motion during breath-holding and the tumor position variation between breath-holds. However, this is still just a conservative estimate of the needed margin because calculating the actual margin would be more complex due to the nature of the motion (e.g. systematic drifts in a particular direction).

In physiological studies it has already been shown decades ago that since there is a continuous uptake of gaseous O₂ without replenishment of CO₂, the lung volume during breath-holding decreases [39–42]. The decrease in total lung volume has been reported to be 200–500 ml/min [39,41]. If we perform a simplistic calculation where we assume the lungs to be two rectangular balloons (dimensions: 100×125×200 mm³, with LR×AP×IS) and the decrease in volume would only result in an upwards motion of the diaphragm. A decrease in lung volume of 500 ml/min (250 ml/min per lung) would result in motion of the diaphragm of 20 mm/min in the superior direction. Even though this is just an estimate of the true motion, the result is similar to what was observed in some of our healthy subjects (chapter 6).

The continuously decreasing lung volume should be present in both inhalation and exhalation breath-holds. However, we observed significantly smaller motion magnitudes during exhalation

Fig. 7.1: Illustration of the tumor motion and the tumor position variation during and between three consecutive breath-holds of one of our patients (patient 3 from chapter 5). The completed motion track of a fiducial during breath-holding is depicted by the colored lines.
breath-holds compared with inhalation breath-holds. Other studies also reported good organ stability during exhalation breath-holding [30,33]. Although these last two studies only used relatively short breath-hold durations of up to 30 s, we would still expect some decrease in lung volume. It may be due to the elastic properties of the diaphragm and/or tension in the diaphragm, when in the exhalation position, that the decrease in lung volume during exhalation breath-hold is partially inhibited. This may explain the differences in motion during inhalation and exhalation breath-holds that we observed. Based on these results, exhalation breath-holds would be most efficient in reducing intrafractional pancreatic tumor motion.

### Prolonged breath-holding durations

Breath-holds of 60 s (used in chapter 6) are already considered to be difficult for patients and therefore 30 s is more often used in patient studies. Introducing more sophisticated breath-holding techniques that involve additional aids for the patients can be used to significantly extend the breath-holding duration. Extended breath-holding durations might allow the CBCT for daily position verification, and irradiation of the patient to be performed within a single breath-hold. This would eliminate the inter-breath-hold tumor position variation and could potentially decrease the time that the patient is on the treatment table.

The tumor motion during prolonged breath-holding can result in substantial tumor displacements during breath-hold. However, by excluding the start of breath-holding (e.g. the first 10 s) through delaying treatment, the tumor motion during the start of breath-holding may be excluded. This may be beneficial since we showed that during this time the tumor motion velocity is greatest.

In the review by Parkes, he describes the various mechanisms that are involved with the physiology of breath-holding and he discusses different strategies to extend the breath-holding duration [42]. By introducing small distractions during breath-holding (e.g. ball squeezing), the breath-hold duration was already increased by 13–19% (from 28 to 32 s for exhalation breath-holds) [43]. A different, highly effective, way to prolong breath-holding durations is to let the subject hyperventilate prior to the breath-hold by using a gas with a 99.5% O₂ concentration instead of room-air [40]. This technique resulted in breath-hold durations of up to 14 minutes. It was also reported that during these prolonged breath-holds there was a decrease in lung volume. On average, it took 13 minutes for the lungs to decrease a volume equal to the vital capacity (the maximum amount of air that can be exhaled after a maximum inhalation).

Prolonged breath-holds have been introduced for radiotherapy as well. Roth et al. investigated the benefit of using pre-oxygenation combined with 1 minute of mechanically induced hyperventilation (i.e. lower concentration of CO₂ in the blood) in order to extend breath-holding duration during radiotherapy in breast cancer patients [44]. They observed an increase in mean breath-holding duration in patients from 40.3 s (when using the conventional breath-holding procedure) to 164.7 s. Nothing was reported about a decrease in lung volume or about the stability of anatomical structures. Parkes et al. also prolonged breath-holding durations by using pre-oxygenation (at 60% O₂) and mechanically induced hyperventilation [45]. They reported an increase in breath-hold duration from 1.4
min (conventional breath-holding) to 2.8 min (breath-holding with pre-oxygenation) and to 5.5 min (breath-holding with pre-oxygenation and 15 minutes of hypocapnia) in healthy subjects. The same protocol was applied to a group of 15 breast cancer patients and they observed a mean breath-holding duration of 5.3 min when applying pre-oxygenation and hypocapnia [46]. During breath-holding they measured the position of the chest surface to quantify the chest deflation due to the decrease in lung volume. They reported settlement of the chest during the first 15 s and a linear motion of up to 2.2 mm/min during the remainder of the breath-hold.

These techniques to induce prolonged breath-holds require training of the patients of one hour [44] up to several sessions on multiple days [46]. Also, mechanical ventilators are required in order to mechanically induce the hypocapnia, along with measurement equipment to measure a variety of physiological parameters (e.g. blood pressure and O2 levels). Introducing prolonged breath-holds for radiotherapy of pancreatic tumors by using these protocols will substantially increase treatment time since for each breath-hold the hypocapnia must be induced. Therefore, it should be investigated whether the benefits of these prolonged breath-holds would outweigh the additional treatment time and patient effort. Also, it should be established whether the system needed to induce the hypocapnia fits in the treatment room while the gantry is rotating and the treatment beam is on.

**Imaging of respiratory-induced motion during treatment**

In chapter 2 we demonstrated that there can be large variations in the daily respiratory-induced pancreatic tumor motion and thus a single pre-treatment respiratory-correlated CT is not sufficient. Therefore, daily imaging by a modality that allows for quantification of the respiratory-induced tumor motion is needed.

A modification of the CBCT system has already been implemented that resulted in the respiratory correlated CBCT, also known as the 4D-CBCT system [48,49]. This system enables the user to measure the respiratory-induced tumor motion while the patient is already on the treatment table. When using the mid-ventilation approach as proposed in chapter 3, daily 4D-CBCT imaging is needed to determine the daily mean respiratory position of the pancreatic tumor. However, it has been shown that the respiratory motion can vary from one respiratory cycle to the next and that there can be drifts during a relatively short period of time [50,51]. The question remains whether the obtained motion from the 4D-CBCT is really representative for the motion during the actual irradiation.

To optimally account for the respiratory-induced tumor motion, real-time imaging during treatment delivery may be required. Studies have been performed using multiple systems that allow for real-time tumor tracking. This can be done using kV imaging during the treatment; machines that are equipped with these imaging systems are for example the Cyberknife system and the VERO system [52–54]. These systems can be used to perform real time tumor tracking or gating, but do require a good tumor contrast or intratumoral fiducials. The Cyberknife system in combination with breath-holding has been used for SBRT treatment of pancreatic cancer [31]. During treatment the patient was asked to perform multiple inhalation breath-holds and the patient was only irradiated
while in breath-hold. The tracking capabilities of the system were used to image the tumor every 1–3 minutes to determine whether the breath-hold position of the tumor had changed and to correct for possible shifts in tumor position. This system can be used to achieve a high geometric accuracy, but using this system for a fractionated treatment, as is often used for pancreatic tumors, would require a long treatment time per fraction. In addition, the positional uncertainty as a result from tumor motion during breath-holding would still require safety margins of at least 3–5 mm.

Another proposed solution is to integrate MR imaging systems into the treatment machines [55,56]. These hybrid systems allow for MR imaging during the actual treatment and the obtained images take advantage of the good soft tissue contrast, which is one of the great benefits of MRI. Studies have been published that focus on a workflow of real-time respiratory-induced motion management of pancreatic tumors [57,58].

**Geometric uncertainties and safety margins**

The margin contribution due to respiratory-induced pancreatic tumor motion varies considerably depending on the used technique (e.g. ITV, mid-ventilation or probabilistic planning). For example, in chapter 3 we showed that a respiratory-induced motion magnitude of 16 mm in the 4DCT resulted in an increase of 4 mm of the PTV margin when using a mid-ventilation approach [59]. If for this particular example an ITV was used, the PTV margin would be increased by the full 16 mm, which would be highly conservative since we showed that the mid-ventilation approach also resulted in good target coverage.

We did not calculate any safety margins to account for the geometric uncertainties during breath-holding. To do so the tumor motion during breath-holding as well as the tumor position variation between consecutive breath-holds would have to be included in the calculation. Since, for the majority of patients and subjects, the tumor motion presented as a slow drift in the superior direction, this tumor motion cannot be considered as a random motion. Therefore, calculation of the necessary margin is not straightforward and has not been performed in this thesis. The effect of the systematic drifts on the dose distributions will not be a simple blurring of the dose, but more a “stretching” of the dose. This could be accounted for by anisotropic margins or by creating a dose gradient within the PTV to account for this drift (similar to probabilistic planning).

Systematic errors can also greatly impact the dose distribution since the effect is persistent during all fractions. Therefore, tackling these systematic errors is at least as important as managing the random errors such as respiratory-induced motion. The most dominant sources of uncertainties, besides the respiratory motion, are delineation uncertainties and the interfractional position variations of the tumor. All these uncertainties must be included when calculating the final PTV margin.

**Delineation and target definition**

For pancreatic cancer the delineation uncertainty can be considerable (an example is shown in Fig. 7.2) [60–63]. These studies showed variations in the GTV delineation between multiple observers, with a maximum ratio of GTV volumes delineated by different observers of 9 (from 13.5 cm³ up
to 122 cm³ for a single patient. Regardless of newly developed guidelines for pancreatic tumor delineation [64], these uncertainties will result in substantial expansions of the PTV because of the necessary safety margins to ensure target coverage [65,66]. No actual margins were calculated in any of the pancreatic tumor delineation studies, but based on the observed standard deviation of approximately 10 mm in each direction [62] a margin of 25 mm would at least be needed to account for the delineation uncertainty. This margin is much larger than the 10 mm that is for example used in the PREOPANC trial [67].

**Interfractional position variation**

Along with the respiratory-induced tumor motion, the interfractional position variation of pancreatic tumors is an important source for geometric uncertainty. Large variations have been observed in the daily pancreatic tumor position relative to the bony anatomy [68–70]. If daily positioning of the patient is performed using daily CBCTs and image registration based on the bony anatomy, mismatches between the actual and expected tumor position of >10 mm may occur in approximately 39% of the fractions [69]. The systematic and random margin contributions for pancreatic patients were reported

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**Fig. 7.2:** Illustration of the inter-observer variation of a pancreatic tumor located in the pancreatic tail and implanted with intratumoral fiducials. Each delineation of a different color represents a different observer.
to be 6.6 and 4.7 mm in superior-inferior direction, respectively [69]. These uncertainties would result in an approximate margin of 20 mm and this margin would only account for the interfractional position variations. However, by using intratumoral fiducials and performing the image registration between CT and CBCT based on these fiducials, the uncertainties can be reduced significantly [69,70]. Theoretically, if the image registration would be perfect the residual uncertainty would be zero.

**Resulting safety margins and treatment volumes**
Combining the delineation and interfractional uncertainties (without the use of intratumoral fiducials) would result in an estimated PTV margin of at least 30 mm. The 10 mm that is now used to account for the geometric uncertainties [67] should be reconsidered since not all institutes use intratumoral fiducials yet and the delineation uncertainty alone requires a margin larger than 10 mm. As a result, previous studies that have looked at the role of dose escalation for pancreatic cancer treatment [71] might have given a misrepresentation of the actual clinical benefit since the used safety margins (PTV was defined as GTV + 10 mm) were too small to correctly account for the geometric uncertainties. Depending on the used method to account for the respiratory-induced motion, the ratio between the discussed uncertainties (i.e. respiratory-induced motion, delineation uncertainty and interfractional position variation) can vary. Especially using the ITV approach, which has been part of the standard clinical care for a relatively long period of time [72,73], results in a large expansion of the treatment volume. However, the notion that the CTV should be covered during the complete respiratory cycle can be considered as conservative and it might be better to discontinue the use of the ITV concept for radiotherapy of pancreatic cancer.

In pancreatic cancer treatment, combining the delineation uncertainty, the interfractional position variations and the intrafractional motion results in large PTVs. It is therefore highly recommended to improve target definition, which might be achieved by using better and more imaging modalities. Also, intratumoral fiducials should be used in combination with daily imaging. Last, the ITV concept should be replaced by either the mid-ventilation concept when free-breathing is desired for the patient, or the intrafractional motion should be reduced by using breath-holding.

**Future perspectives**
Since the perspectives for pancreatic cancer patients are still extremely poor it is important to continue pursuing new possibilities in pancreatic cancer treatment and to optimize current treatment options. Future research should focus on reducing the toxicity resulting from radiotherapy.

**Imaging for better target definition**
Dual energy CT might provide better contrast of pancreatic tumors and could therefore be used to better identify the primary GTV [74]. MR imaging is also known to be potentially beneficial for the identification of the primary pancreatic tumor as well as the tumor extension [75]. Recent work also showed the influence of the used intratumoral fiducials on the quality of MR images and the potential use of the fiducials for other purposes such as positioning [76]. With the ongoing development of
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new MRI techniques (e.g. diffusion weighted imaging), the use of MRI may reduce the inter-observer pancreatic tumor delineation variation considerably [77–79]. Therefore, it is becoming more important to integrate MRI in the radiotherapy workflow for pancreatic cancer.

Imaging for treatment response monitoring
Randomized controlled trials that stratify between conventional and experimental treatments should preferably be combined with a concurrent imaging study to monitor treatment response. The obtained data can then be used to determine criteria based on patient specific parameters that, in the future, can be used to determine prior to treatment whether a specific treatment would be beneficial for that patient [80,81].

Response monitoring is typically performed using CT imaging, radiographic indicators such as tumor size and tumor infiltration in nearby structures are used, but these may not be ideal [82,83]. Using modalities that provide more functional information, such as PET-CT and diffusion weighted MRI, can result in more accurate models when it comes to predicting or evaluating treatment response [84–86]. The unavoidable respiratory-induced motion during a PET-CT is already the subject of numerous studies [87,88]. However, dedicated treatment response imaging studies to determine patient groups that might respond better to certain treatments should be initiated, as these studies could lead to a more efficient treatment.

The currently open Dutch national PREOPANC trial, in which the potential benefit of preoperative radiochemotherapy for pancreatic cancer is being investigated in a multi-institutional randomized controlled way [67], is combined with such an imaging study [89]. This study runs parallel to the PREOPANC trial and focusses on response imaging of the two arms of the PREOPANC trial, by using [18F]HX4 in combination with PET and functional MRI sequences such as diffusion weighted imaging, to establish the level of hypoxia of pancreatic tumors [89]. To verify whether hypoxia and diffusion of the actual tumor is determined and to look at the micro-environment of the tumor, the imaging data are compared with the pathology of resected specimens [90]. This can be used to achieve a high geometric accuracy and thus establish an accurate map of the tumor heterogeneity (i.e. hypoxic tumor regions may be identified).

Dose painting
By using the MR scanners’ capability to perform functional imaging, we may be able to better characterize the tumor [91]. We could determine parts of the tumor that respond well to a higher dose or parts that are more resistant, and give those areas an additional boost [92]. Such a dose painting strategy might improve local control and even survival [93]. However, dose painting requires a very high accuracy because of local high dose regions and concurrent steep dose gradients, which may be difficult to achieve under the presence of the respiratory-induced motion. So, before implementing these dose painting strategies we should improve our respiratory-induced motion management and exhalation breath-holding might be best suitable to preserve the steep dose gradients needed for dose painting.
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Big data
It might also be beneficial to use data from previous pancreatic cancer patients that have received radiotherapy. For all these patients disease information, treatment plans and outcome should be available and this information could be used to optimize the treatment of future patients. Using previous patient data and analyzing tumor patterns and treatment outcome could lead to a major optimization of radiotherapy [94]. For example, the dose to OARs could be reduced by determining the best possible dose distribution for a pancreatic cancer patient based on a large set of previous treatments plans [95]. So, to be able to optimize the treatment of future patients we should systematically save all patient data and this data should be shared among research groups.

Imaging during treatment
Image-guided treatment techniques, both new and optimizations of current techniques, will play a major role in improving the accuracy of radiotherapy and thus reducing the PTV margins. By using intratumoral gold fiducials we are able to pinpoint the tumor location, but the tumor extent is still based on pre-treatment imaging. The introduction of MR-guided treatment machines allows visualization of the tumor during irradiation [55,56]. Using daily MR scans would allow for daily tumor visualization and could therefore aid in measuring daily tumor extent and adapting to possible changes in anatomy or tumor size.

Imaging during the actual delivery of the treatment also allows for tumor tracking and or gating. These techniques will increase the treatment accuracy and are robust against variations in the intrafractional motion. Tracking and gating can be done using highly sophisticated systems such as MR-guided systems [55,56], specialized systems such as Cyberknife and VERO [52,54,96] or by using conventional systems combined with modified software to allow imaging and image processing during irradiation [97–99]. Real time imaging in combination with tracking and/or gating can increase treatment accuracy considerably and might play a crucial role in the future of pancreatic cancer radiotherapy.

Hyperthermia
There are also indications that combining hyperthermia with radiotherapy and/or chemotherapy may have a positive effect on local control and overall survival for pancreatic cancer patients [100,101]. Pancreatic tumors are typically hypoxic tumors, which in part may explain their resistance to both radiation and chemotherapy. Hyperthermia typically enhances the effects of both radiation and chemotherapy, particularly in hypoxic tumor areas, for example by stimulating blood flow. Hyperthermia is a safe technique that has almost no additional negative side effects. This modality is not widely used even though there is quite some evidence of its benefit. There are also several clinical studies suggesting a positive effect in pancreatic cancer [100–107]. The use of hyperthermia in pancreatic cancer treatment should be investigated in future trials.
Particle therapy
The potential benefits of using particle (i.e. protons or carbons) therapy for pancreatic cancer patients have been under investigation for several years now and these studies show promising results [108–114]. The biggest advantage of using these particle beams instead of photons is the fact that considerably more conformal dose distributions can be achieved, resulting in lower dose to surrounding OARs. The lower dose to the healthy tissue potentially allows for dose escalation studies without increasing the NTCP.

The effects of geometric uncertainties and especially the intrafractional motion for particle therapy can be considerable. This is mostly because the location of the Bragg peak greatly depends on the density of the tissue (e.g. bone, air or water) in the beam path. If the tumor for example has a shift in position relative to the expected tumor position, it is possible that the surrounding tissues receive the high dose that was planned on the tumor, but also the target coverage could seriously get degraded. Several studies have investigated the effects of intrafractional motion on the dose distribution and they all reported potentially severe dosimetric variations as a result of the intrafractional anatomical variations [115,116].

Robust optimization can be used to account for random range and setup uncertainties [117,118]. The effects of the respiratory-induced tumor motion on intensity modulated proton therapy (IMPT) dose distributions are more difficult to account for. For example, there are the interplay effects due to the motion of the tumor and the scanning of the spot-sized proton beam over the tumor volume, which can compromise target coverage and dose uniformity [119,120].

Accounting for the respiratory-induced tumor motion during IMPT can be challenging and multiple solutions have been proposed. The easiest approach still seems motion reduction by using techniques such as breath-holding [121,122]. Gating could also be used to deliver the treatment only when the tumor is at a specific and pre-defined position, often the exhale tumor position is used [123]. A technically more challenging approach is to use tumor tracking during delivery of the treatment [124,125]. This technique, although promising, requires a modification of the regular treatment machines that will not be available in all clinics and implementing it might prove highly difficult. For pancreatic cancer patients, breath-holding and gating techniques are most feasible and easiest to implement in combination with particle therapy. Also, because of the good preliminary results of proton therapy for these patients, we should consider pancreatic cancer as an indication for proton therapy.

Conclusions
Radiotherapy is an important link in the treatment chain of pancreatic cancer, but respiratory-induced tumor motion could limit the treatment efficacy. We showed that there can be a large variation in the daily respiratory-induced pancreatic tumor motion magnitude and that a single pre-treatment 4DCT is often not sufficient to predict daily tumor motion. The first step towards better respiratory-induced motion management of pancreatic tumors is to use modern treatment planning techniques instead of a motion-encompassing technique. Mid-ventilation and probabilistic planning are promising
candidates that allow for significant dose reductions to surrounding healthy tissues. However, these techniques still depend on the single pre-treatment 4DCT.

Breath-holding could also be used to reduce intrafractional tumor motion, but because of the remaining geometric uncertainties an optimization of the breath-holding protocols is needed. If breath-holding is the technique of choice for reducing or eliminating the respiratory-induced tumor motion during radiotherapy, at least exhalation breath-holds should be used. We observed a significant decrease in pancreatic motion during exhalation breath-holding and other studies reported only small tumor position variations between consecutive exhalation breath-holds. Future research is should be performed to determine the safety margins that would be needed when using breath-holding in the clinic, based on the tumor motion during breath-holding and the tumor position variation between breath-holds. Preferably, extended breath-holding durations should be used as well. If no system is available to mechanically induce hypocapnia, at least pre-oxygenation could be used since this has been shown to already improve breath-holding durations.
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