Respiratory motion management for radiotherapy of pancreatic cancer patients

Lens, E.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 2

Differences in respiratory-induced pancreatic tumor motion between 4D treatment planning CT and daily cone beam CT, measured using intratumoral fiducials

Eelco Lens¹, Astrid van der Horst¹, Petra S Kroon², Jeanin E van Hooft³, Raquel Dávila Fajardo¹, Paul Fockens³, Geertjan van Tienhoven¹, Arjan Bel¹

¹Department of Radiation Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
²Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, the Netherlands
³Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Adapted from: Acta Oncologica 2014;53:1257–1264
Chapter 2

Abstract

Background and aim
In radiotherapy, the magnitude of respiratory-induced tumor motion is often measured using a single 4-dimensional CT (4DCT). This magnitude is required to determine the internal target volume. The aim of this study was to compare the magnitude of respiratory-induced motion of pancreatic tumors on a single 4DCT with the motion on daily cone beam CT (CBCT) scans during a 3 to 5-week fractionated radiotherapy scheme. In addition, we investigated changes in the respiratory motion during the treatment course.

Materials and methods
The mean peak-to-peak motion (i.e. magnitude of motion) of pancreatic tumors was measured for 18 patients using intratumoral gold fiducials visible on CBCT scans made prior to each treatment fraction (10–27 CBCTs per patient; 401 CBCTs in total). For each patient, these magnitudes were compared to the magnitude measured on 4DCT. Possible time trends were investigated by applying linear fits to the tumor motion determined from daily CBCTs as a function of treatment day.

Results
We found a significant ($p \leq 0.01$) difference between motion magnitude on 4DCT and on CBCT in superior-inferior, anterior-posterior and left-right direction, in 13, 9 and 12 out of 18 patients, respectively. In the anterior-posterior and left-right direction no fractions had a difference $\geq 5$ mm. In the superior-inferior direction the difference was $\geq 5$ mm for 17% of the 401 fractions. In this direction, a significant ($p \leq 0.05$) time trend in tumor motion was observed in 4 out of 18 patients, but all trends were small (-0.17–0.10 mm/day) and did not explain the large differences in motion magnitude between 4DCT and CBCT.

Conclusion
A single measurement of the respiratory-induced motion magnitude of pancreatic tumors using 4DCT is often not representative for the magnitude during daily treatment over a 3 to 5-week radiotherapy scheme. For this patient group it may be beneficial to introduce breath-hold to eliminate respiratory-induced tumor motion.
Introduction

Neoadjuvant radiochemotherapy has a potential benefit in resectable and borderline resectable pancreatic cancer [1]. This treatment, however, is highly toxic due to the high radiation dose levels to surrounding organs at risk (OARs) such as stomach, duodenum and kidneys. Reducing the size of the planning target volume (PTV) may help spare these OARs.

The size of the PTV is partially determined by the amount of respiratory-induced motion of the tumor. The respiratory-induced motion magnitude, investigated for various tumor sites [2,3], is for the pancreas reported to be 5–15 mm [2,4–8]. The motion magnitude is often measured only once before treatment planning (e.g., using 4DCT). However, tumor motion can vary from day to day and even from one respiratory cycle to the next, so a single measurement can be misrepresenting and might lead to insufficient target coverage [9]. Therefore, thorough investigation is needed to determine whether the tumor motion as represented on planning CT is a good predictor for the tumor motion during daily treatment.

For the pancreas, very few studies have investigated the predictive value of 4DCT [10,11]. Ge et al. investigated 3–5 respiratory cycles per measurement [11]. However, respiratory motion is known to change over short periods of time [12,13]. Minn et al. used hundreds of cycles per measurement, but compared each 4DCT with only a single (Cyberknife) fraction [10]. With respiratory motion also changing over longer periods of time [12,13], their work is not representative for fractionated treatments of several weeks [10]. Daily CBCTs enable investigation of magnitudes of and trends in the respiratory-induced pancreatic tumor motion over the complete course of treatment.

We studied the respiratory-induced tumor motion in 18 pancreatic cancer patients using 4DCT and daily CBCTs over a 3 to 5-week fractionated treatment. Tumor motion was measured using intratumoral gold fiducials. The aim of this study was to compare the magnitude of respiratory-induced motion of pancreatic tumors using a single 4DCT, with daily CBCT scans during a fractionated radiation treatment scheme. In addition, we investigated trends in the respiratory motion during the treatment course.

Materials and methods

Patients and treatment

From October 2010 to August 2013, 18 consecutive patients (11 males and 7 females) with a pancreatic carcinoma, who had received a 4DCT scan and were treated with radiotherapy, were included in this retrospective study. All patients, with a mean age of 65 years (range, 46–79), underwent an endoscopic ultrasound-guided implantation of 2–4 intratumoral gold fiducial markers to enable daily CBCT position verification. Three patients received Gold Anchor fiducials (Naslund Medical, Huddinge, Sweden; thickness, 0.28 mm; length, 1 cm) and the remaining patients were implanted with Visicoil markers (RadioMed, Barlett, TN; thickness, 0.35 mm; length, 0.5–2.0 cm). Patient 16 received a Gold
Anchor as well as a Visicoil fiducial. Patients 1–16 were also included in earlier studies of our group on interfractional tumor position variations [14,15]. The corresponding patient numbering in these papers [14,15] with the present paper can be found in Appendix B Table B2.1. Marker motion is representative for tumor motion since no migration of the fiducials over the course of treatment was observed [14].

Patient 18 had a tumor in the pancreatic tail, patient 4 in the pancreatic body/tail, patient 9 in the pancreatic body and all others in the pancreatic head. Patients were treated with radiochemotherapy using 3 different schemes. For patients 9, 14 and 16 the prescription dose was 28×1.8 Gy, for patients 17 and 18 it was 15×2.4 Gy and for all other patients it was 25×2.0 Gy. All treatment schemes were combined with concurrent chemotherapy (Appendix B Table B2.1).

All included patients received a 4DCT scan (LightSpeed RT16 system, General Electric Company, Waukesha WI, USA), taken under normal breathing conditions. The respiratory cycle was divided into 10 bins, resulting in 10 4DCT phase scans (slice thickness, 2.5 mm; pixel size, 1.0×1.0 mm2). For patients 1 and 3 the 4DCT scan was made at a later stage than the planning CT scan (on day 30 and 10, respectively, with the planning CT on day 0). All patients received CBCT imaging (Synergy, Elekta Oncology systems, Crawley, UK) prior to each treatment fraction. Thirty-five of the planned treatment fractions were not delivered due to early termination of treatments and 3 CBCTs were not retrievable, resulting in 10–27 scans per patient (mean, 22; 401 CBCTs in total).

The magnitude of respiratory-induced marker motion (MM), defined as the mean peak-to-peak motion of the markers due to respiration along one of the main axes, was determined for the 4DCT scans (MM_{4DCT}) as well as for each CBCT (MM_{CBCT}), in superior-inferior (SI), anterior-posterior (AP) and left-right (LR) direction.

4DCT
A 4DCT scan took about 90 seconds and for every couch position a single respiratory cycle was used. To measure MM_{4DCT}, the 10 phase scans were individually matched. This was done by using the end-inhale phase scan as a reference and performing rigid registrations of the other 9 phase scans to this reference scan, based on the markers and using translations only. The obtained translation values gave the excursion of the markers throughout the respiratory cycle in all three directions. In each direction, the difference between the most extreme translations was considered as MM_{4DCT}.

CBCT
The CBCT scans were reconstructed from kV projection images that were made while the system rotated around the patient. Each scan took approximately 2 minutes and produced about 700 projection images over a full 360° rotation, during which the patient was breathing freely. To determine MM_{CBCT}, we made reconstructions of the end-inhale (EI) and end-exhale (EE) phases. We selected the projections belonging to each of these phases by extracting the respiratory signal from the projection images.

Extraction of the respiratory signal was done using an in-house developed program written
in MATLAB (The MathWorks Inc., Natick, MA, USA). The sum of the pixel values over a region of interest (ROI) within the projections was plotted against the gantry angle (Figs. 2.1a–b). Three main components contributed to the obtained signal: gantry angle (causing changes in attenuation), cardiac motion and respiratory-induced motion [16,17]. The contribution of the gantry rotation was filtered out by applying a moving average filter (sliding-window width of 31 data points) and subtracting this filtered signal from the original signal. The contribution of the cardiac motion was filtered out by applying a second moving average filter (sliding-window width of 5 data points), leaving the respiratory signal (Figs. 2.1c–d). A similar method was described by Kavanagh et al. [16].

The acquired signal contained phase and frequency of the respiratory signal, but no information on the amplitude of respiratory-induced motion of the markers. By selecting the projection images corresponding to the peaks and troughs in the signal, 3D CBCT reconstructions were made of the patient in the EE and the EI phase, respectively. Both reconstructions contained between 20–40 projections depending on the frequency of respiration. Even though this resulted in low-quality reconstructions,
blurred in part due to the cardiac motion, the fiducials remained clearly visible. We matched the reconstructions to the planning CT by rigid registration on the fiducial markers, using translations only. The differences in translation values for the two registrations gave $MM_{\text{CBC}}$ in all three directions.

Motion magnitude measurement validation

For validation of the performance of the $MM_{\text{CBC}}$ procedure, MM was also obtained directly from individual projections ($MM_{\text{CBproj}}$) using a procedure described by Marchant et al. [18]. By manually selecting the positions of the fiducials in every single projection image and applying a coordinate transformation to go from CBCT-panel coordinates to patient coordinates, the true 3D marker motion could be determined. After the marker motion during CBCT acquisition was obtained, the peak-to-peak motion of every respiratory cycle was determined and then averaged to yield $MM_{\text{CBproj}}$. The marker motion in the SI direction is along the axis of the gantry rotation and can therefore be measured during the complete CBCT acquisition. In LR and in AP, the motion is perpendicular to this axis and can be measured during small parts of the CBCT acquisition only; therefore LR and AP were not taken into account for this validation.

This procedure was very time consuming (about 10 hours per CBCT). $MM_{\text{CBproj}}$ was measured for 7 fractions from 5 patients, randomly chosen, and we checked the performance of the (MATLAB) $MM_{\text{CBC}}$ program by analyzing the absolute differences between $MM_{\text{CBC}}$ and $MM_{\text{CBproj}}$ in the SI direction for each CBCT.

Comparison 4DCT and CBCT data

In order to determine whether $MM_{\text{4DCT}}$ was a good predictor for $MM_{\text{CBC}}$, we tested for each patient whether the mean $MM_{\text{CBC}}$ was equal to $MM_{\text{4DCT}}$ using a one-sample Wilcoxon rank sum test. To examine the relevance of the difference between $MM_{\text{4DCT}}$ and $MM_{\text{CBC}}$, we calculated for each patient the absolute difference between $MM_{\text{4DCT}}$ and each $MM_{\text{CBC}}$ value ($\Delta$) in all three directions separately and determined the numbers of fractions for which $\Delta \geq 3$ mm and $\Delta \geq 5$ mm. Also, a paired Student’s $t$-test was used to evaluate the difference between the mean $MM_{\text{4DCT}}$ and the average of the mean $MM_{\text{CBC}}$ values (normality of the data was tested using the Shapiro-Wilk test).

To test whether $MM_{\text{CBC}}$ was constant over the course of treatment, we plotted for each patient $MM_{\text{CBC}}$ as a function of treatment day and applied linear fits to determine the behavior of $MM_{\text{CBC}}$ over time. All analyses were performed in the three directions and all statistical analyses were done using R version 3.0.1 (R Foundation for Statistical Computing, USA).

Results

The mean $MM_{\text{4DCT}}$ was 8.3 (SD 3.3) mm, 2.9 (1.0) mm and 2.4 (1.1) mm in SI, AP and LR direction, respectively. The mean $MM_{\text{CBC}}$ over all patients was 7.0 (SD 2.8) mm, 2.2 (0.8) mm and 1.5 (0.8) mm, respectively (Fig. 2.2).
In the SI direction, the mean absolute difference, after post-processing of the data, between $\text{MM}_{\text{CBCT}}$ and $\text{MM}_{\text{CBproj}}$ over the 7 evaluated CBCTs was 0.6 mm (details can be found in Appendix A). This was used as a validation for the used measurement procedures.

In the SI direction, tumor motion on 4DCT was significantly different from the mean motion during the treatment itself for 13 out of 18 patients ($p \leq 0.01$; Table 2.1). We found $\Delta \geq 3$ mm for 36% and $\Delta \geq 5$ mm for 17% of the 401 fractions. The mean $\text{MM}_{\text{4DCT}}$ was significantly larger than the average mean $\text{MM}_{\text{CBCT}}$ ($p=0.012$). $\text{MM}_{\text{4DCT}}$ seems therefore not a good predictor for daily tumor motion when used for creating PTVs.

In the AP and LR direction, tumor motion on 4DCT was significantly different from the mean motion during the treatment itself for 9 and 12 out of 18 patients, respectively ($p \leq 0.01$). $\Delta$ was $\geq 3$ mm for 6% and 5%, respectively, and in both directions there were no fractions with $\Delta \geq 5$ mm. The mean $\text{MM}_{\text{4DCT}}$ was significantly larger than the average mean $\text{MM}_{\text{CBCT}}$ in both directions, $p=0.021$ and $p=0.001$ in AP and LR, respectively.

We found that 16, 10 and 9 out of the 18 trend lines had a negative slope (Fig. 2.3 and Appendix C Figs. C2.1–C2.3), in SI, AP and LR, respectively, indicating that the respiratory-induced motion magnitude decreased over time. The largest slope that was found was -0.17 mm/day for patient 15 in the SI direction. Nine patients had a significant slope ($p \leq 0.05$) in 1 direction; for 3 of these patients the absolute slope was larger than 0.1 mm/day.

**Fig. 2.2:** 4DCT (red solid lines) and CBCT data (boxplots) of respiratory-induced fiducial marker motion magnitude (MM) in (a) superior-inferior, (b) anterior-posterior and (c) left-right direction.
Chapter 2

Discussion

We compared tumor motion in pancreatic cancer patients on 4DCT to tumor motion on daily CBCT using intratumoral gold fiducials. The present study was the first to include such a large number of patients and use daily measurements during a 3 to 5-week treatment course. This resulted in an extensive dataset with up to 28 data points per patient, allowing us to make a comprehensive comparison of the tumor motion during treatment planning and treatment and to detect time trends in tumor motion during treatment, which have not been reported for pancreatic tumors so far. The mean motion magnitude was 8.3 (SD 3.3) mm on 4DCT and 7.0 (SD 2.8) mm on CBCT. Our study showed that for the majority of the evaluated patients the tumor motion at treatment planning was not representative for the tumor motion during a 3 to 5-week fractionated treatment.

The algorithm by Kavanagh et al., similar to our algorithm used to extract the respiratory signal

<table>
<thead>
<tr>
<th>Patient #</th>
<th># of CBCTs</th>
<th># (Δ ≥3 mm), (% of fractions)</th>
<th># (Δ ≥5 mm), (% of fractions)</th>
<th>MM_{4DCT} compared to mean MM_{CBCT} (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>17 (68%)</td>
<td>2 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0.69</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.35</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>12 (48%)</td>
<td>1 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>24 (96%)</td>
<td>22 (88%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0020</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>9 (36%)</td>
<td>1 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.0005</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>2 (8%)</td>
<td>0 (0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>11</td>
<td>18</td>
<td>17 (94%)</td>
<td>9 (50%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>23 (92%)</td>
<td>21 (84%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>13</td>
<td>25</td>
<td>9 (36%)</td>
<td>1 (4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.08</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
<td>7 (28%)</td>
<td>0 (0%)</td>
<td>0.57</td>
</tr>
<tr>
<td>16</td>
<td>27</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>17</td>
<td>15</td>
<td>10 (67%)</td>
<td>6 (40%)</td>
<td>0.0076</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>9 (60%)</td>
<td>4 (27%)</td>
<td>0.0026</td>
</tr>
<tr>
<td>All</td>
<td>401</td>
<td>144 (36%)</td>
<td>67 (17%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CBCT, Cone Beam CT; MM_{4DCT}, tumor motion magnitude on 4DCT; MM_{CBCT}, tumor motion magnitude on CBCT; Δ, absolute difference between MM_{4DCT} and MM_{CBCT}; bold indicates p<0.01.
from the CBCT projections, has been shown to compare well to the Amsterdam shroud procedure [16]. We validated our method to determine \( \text{MMC}_{\text{CBCT}} \) by comparing \( \text{MMC}_{\text{CBCT}} \) to \( \text{MMC}_{\text{CBproj}} \) for 7 CBCTs and found small differences. As an additional validation we determined \( \text{MMC}_{\text{CBCT}} \) for a chosen fixed magnitude of motion. This was done by making two 3D-CBCT reconstructions from projections for which the marker was at one of two preselected positions (e.g. -4 and 4 mm in Fig. 2.4b, so that the expected \( \text{MMC}_{\text{CBCT}} \) was 8 mm) and compared the obtained \( \text{MMC}_{\text{CBCT}} \) to this fixed magnitude of motion. This was done for 2 CBCTs and 3 values of \( \text{MMC}_{\text{CBCT}} \) (6, 8 and 10 mm). Differences between the expected \( \text{MMC}_{\text{CBCT}} \) and the determined \( \text{MMC}_{\text{CBCT}} \) were small (up to 0.3 mm) when using these selected projections. This residual error was most likely due to uncertainties in the image registration.

The used algorithm did not always identify the correct projections as EE or EI. For 2 CBCTs we manually selected the correct EE and EI projections using the marker motion shown in Figs. 2.4b–c and found a maximum discrepancy of 0.3 mm for \( \text{MMC}_{\text{CBCT}} \). Even though the reconstructions were in a specific respiratory phase, the markers may still have been blurred due to the variation in marker position in EE or EI during a single CBCT acquisition; Fig. 2.4b shows a variation in EI marker position of 18 mm. This blurring combined with the inability of the program to always select the correct projections led to an uncertainty estimated to be <1 mm (SD) in the values of \( \text{MMC}_{\text{CBCT}} \). For the detection of fiducials in the CBCT projection images no automated procedures (e.g. as proposed by Fledelius et al. [19]) were used. Implementing such procedures would be difficult for this patient group because small fiducials, as used in this study, produce very low contrast on the projection images. Also, 12 out of 18 patients had a biliary stent very close to the fiducials, further compromising automatic marker detection for these patients.

The measured respiratory-induced motion of pancreatic tumors was similar to the 5–15 mm
Chapter 2

reported in the literature [2,4–8]. Our results show that the respiratory-induced motion during 4DCT is often not representative for the motion during daily CBCT measurements. No additional analyses were performed to determine dependences on tumor location or stage of the disease, as patient numbers were too small to do so. Only 3 patients had a tumor located somewhere else than the pancreatic head.

In the SI direction, MM$_{\text{4DCT}}$ was significantly different from the mean MM$_{\text{CBCT}}$ in 13 out of 18 patients. This was in agreement with two papers that compared the 4DCT results of respiratory-induced motion of the pancreas to daily measurements [10,11]. Both found significant differences between tumor motion at treatment planning and during daily treatment, as we did for considerably more measurements per patient and during all daily fractions of the 3 to 5-week treatment, with each measurement consisting of at least 20 respiratory cycles.

Respiratory-induced motion is not very regular or uniform. The peak-to-peak motion can vary greatly during CBCT acquisition due to irregular breathing [5] and a single value for MM is not necessarily representative for the entire motion. In addition, the actual MM during irradiation can again be different from the MM during CBCT acquisition. Also for 4DCT, irregular breathing patterns can influence the measured MM. For liver and lung patients, with a mean peak-to-peak motion of 20 mm, SDs of mean tumor location of 1.7 and 3.0 mm were found in EE and EI, respectively, due to

---

Fig. 2.4: Marker motion in the superior-inferior direction during a CBCT, for 3 fractions (a–c). Circles indicate projections selected by the program to make end-inhale (open) and end-exhale (closed) phase reconstructions.
irregular breathing patterns [20]. This could lead to a suboptimal treatment when the incorporation of respiratory-induced motion in the PTV is based on such a single measurement. What can be seen from our data is that the fiducial position in EE is much more reproducible than in EI; this is clearly visible in Fig. 2.4.

For 10 patients the MM_{4DCT} was significantly larger than the MM_{CBCT} in the SI direction. Also, the mean MM_{4DCT} was significantly larger than the average mean MM_{CBCT} for this patient group. Overestimating the respiratory-induced motion during treatment would lead to too large a PTV. The observation that tumor motion during 4DCT was larger than tumor motion during treatment has been reported for other tumor sites as well, for example for lungs by Britton et al., who reported that a single 4DCT may not be sufficient to determine an ITV for highly mobile tumors [21]. In addition, a considerable variation in absolute amplitude of the tumor motion in the lung was reported [22]. For a 30 minute period directly following a 4DCT scan, it was found that the scan could sufficiently predict respiratory-induced lung tumor motion [23].

The observed time trends were small and did not explain the discrepancy between treatment planning and daily treatment. The largest significant slope resulted in a decrease of MM_{CBCT} of 5.8 mm, in SI direction, over the complete course of treatment (patient 15). The negative slopes could be due to patients relaxing more as the treatment progresses, as was also speculated by Seppenwoolde et al. [3]. Other papers reported non-significant time trends in the magnitude of respiratory-induced motion over time, for example in lung cancer patients [24].

Using MM_{4DCT} as a measure for daily tumor motion could lead to sub-optimal PTVs. Our results suggest that introducing a form of active breath control such as tracking or voluntary breath-hold may be beneficial for irradiation of patients with pancreatic cancer. That way, the differences in motion magnitude between 4DCT, used for margin determination, and daily treatment could be eliminated. A remaining margin of 5 mm is reported to be sufficient to account for all position variations in EE breath-hold for pancreatic cancer patients [25].

Conclusion

The respiratory-induced motion of pancreatic tumors measured with 4DCT was often not representative for the tumor motion during treatment measured using daily CBCTs, as they differed significantly in the majority of patients. Also, tumor motion was variable throughout the treatment. Time trends, however small, suggested that tumor motion can change as the treatment progresses. Our results show the limitations of using a single 4DCT to take into account the patient specific respiratory-induced pancreatic tumor motion when doing treatment planning. Introducing breath-hold may be beneficial for pancreatic cancer patients.
Appendix A: Addition to the validation of measurement results

In the S-I direction, the mean absolute difference between $\text{MM}_{\text{CBCT}}$ and $\text{MM}_{\text{CBproj}}$ over the 7 evaluated CBCTs, used as a validation for the used measurement procedures, was 0.8 mm (range, 0.3–2.0 mm). The maximum absolute difference was 2.0 mm. This maximum difference of 2.0 mm ($\text{MM}_{\text{CBproj}} = 16.4$ mm and $\text{MM}_{\text{CBCT}} = 14.4$ mm, patient 14 fraction 1) was mainly due to 2 outlying inhalation peaks and measured 0.3 mm after removing these 2 outliers (Fig. 2.4b; gantry angles 37° and 60°). In that case the mean absolute difference over the 7 CBCTs changed from 0.8 mm to 0.6 mm (range, 0.1–1.5 mm). Note that the removal of outliers is not possible without the time-consuming determination of the respiratory-induced motion from CBCT projection images.
### Appendix B: Patient information

#### Table B2.1: Prescribed radiation and chemotherapy schemes

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Patient # in Ref. 14 and 15</th>
<th>Radiation scheme</th>
<th>Weekly Gemcitabine</th>
<th>Weekly Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>9</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>11</td>
<td>28×1.8 Gy</td>
<td>300 mg/m²</td>
<td>1.5–2.0 mg/kg</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>13</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>28×1.8 Gy</td>
<td>300 mg/m²</td>
<td>1.5–2.0 mg/kg</td>
</tr>
<tr>
<td>15</td>
<td>17</td>
<td>25×2.0 Gy</td>
<td>300 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>16</td>
<td>18</td>
<td>28×1.8 Gy</td>
<td>300 mg/m²</td>
<td>1.5–2.0 mg/kg</td>
</tr>
<tr>
<td>17</td>
<td>22</td>
<td>15×2.4 Gy</td>
<td>1000 mg/m²</td>
<td>NA</td>
</tr>
<tr>
<td>18</td>
<td>23</td>
<td>15×2.4 Gy</td>
<td>1000 mg/m²</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, Not Applicable;

†Patient included in the PARAGE study, a multi-center phase I/II clinical trial in the Netherlands (EudraCT No. 2010-018327-26);

‡Patient included in the PREOPANC study, a multi-center phase III clinical trial in the Netherlands (EudraCT No. 2012-003181-40).
Appendix C: Supplementary figures

Fig. C2.1: MM_{CBCT} values (closed symbols) in superior-inferior direction for all patients, plotted as function of treatment day (day 0 is the day of planning CT). Lines are linear fits to the MM_{CBCT} data; slopes (mm/day) are indicated in the legends (* \( p < 0.05 \); ** \( p < 0.01 \); *** \( p < 0.001 \)). MM_{4DCT} values (open symbols) were not included in the fit.
Tumor motion at treatment planning and during daily treatment

Fig. C2.2: $M_{\text{M} \text{CCT}}$ values (closed symbols) in anterior-posterior direction for all patients, plotted as function of treatment day (day 0 is the day of planning CT). Lines are linear fits to the $M_{\text{M} \text{CCT}}$ data; slopes (mm/day) are indicated in the legends (* $p<0.05$; ** $p<0.01$; *** $p<0.001$). $M_{\text{M} \text{DCT}}$ values (open symbols) were not included in the fit.
Fig. C2.3: MM_CBCT values (closed symbols) in left-right direction for all patients, plotted as function of treatment day (day 0 is the day of planning CT). Lines are linear fits to the MM_CBCT data; slopes (mm/day) are indicated in the legends (* p<0.05; ** p<0.01; *** p<0.001). MM_DCCT values (open symbols) were not included in the fit.
Tumor motion at treatment planning and during daily treatment

References


Chapter 2


