Respiratory motion management for radiotherapy of pancreatic cancer patients
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Chapter 1

General introduction
Chapter 1

Pancreatic cancer

The pancreas is part of the digestive system. It is a glandular organ that produces several enzymes for the digestion of fat and proteins, and it secretes hormones such as insulin. The pancreas is located in the upper abdomen and lies partly behind the stomach and below the liver (Fig. 1.1). The pancreas is divided into the pancreatic-head, -body and -tail. The common bile duct runs through the pancreatic head where it comes together with the (exocrine) pancreatic duct to flow into the duodenum. In close proximity of the pancreatic head and body lie a number of important blood vessels, such as the superior mesenteric artery the superior mesenteric vein, the portal vein, the common hepatic artery and the celiac trunk.

![Fig. 1.1: Transverse computed tomography (CT) slice of the upper-abdominal region illustrating the location of the pancreas relative to the liver and the stomach. This patient was also implanted with a biliary stent to remedy the obstruction of the bile duct due to the tumor mass in the pancreatic head.](image)

Prevalence and treatment

In the Netherlands, pancreatic cancer was the tenth and eighth most common cancer type in men and women in 2015, respectively, with a combined total of 2284 new cases [1]. With a 1-year survival rate of 24% and a 5-year survival rate of 7%, it is one of the most lethal cancer types [1].

Currently, the only potentially curative treatment is surgery, and whether this procedure can be performed depends on the staging of the disease, including the involvement of neighboring healthy tissues such as large blood vessels. Only 15–20% of all patients are eligible for surgery. Of these patients, about 35% turn out to have irresectable tumors and/or have positive resection margins [2]. If the resected specimen has clear surgical margins, the median overall survival of the patient is around 23 months [3].

Adding systemic treatment has been shown to be beneficial as it increases overall survival [4–7]. Postoperative chemotherapy is considered the standard treatment in Europe. In the United
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States of America, radiochemotherapy has been advocated in some large studies [8–10]. Preoperative radiochemotherapy has been suggested to be better than postoperative radiochemotherapy [9,11]. Preoperative radiochemotherapy also potentially increases the resection rate and the rate of microscopically complete resection, hence potentially improving overall survival [12–15]. The poor outcome of pancreatic cancer, even when resectable or borderline resectable, and the potential advantage of preoperative radiochemotherapy prompted the National multidisciplinary Dutch Pancreatic Cancer Group (DPCG) to initiate a controlled randomized phase three study: the PREOPANC trial [16]. The control arm of the PREOPANC trial consists of standard explorative surgery and in case of successful resection followed by six courses of full dose gemcitabine chemotherapy. This is compared to the experimental arm that consists of preoperative full dose gemcitabine based radiochemotherapy, followed by explorative surgery and in case of successful resection followed by the remainder of gemcitabine based chemotherapy. The study aims for a six months improvement of median survival by intention to treat and requires 244 patients. The study started in April 2013, and has accrued 175 patients up to July 2016 [16].

External beam radiotherapy

Aim of radiotherapy

Radiotherapy is one of the most important pillars of cancer treatment. During radiotherapy the patient is treated by ionizing radiation, which damages the cancerous cells and induces cell death by inducing DNA damage in the form of single or double stranded breaks.

The cell damage not only occurs in the tumor, but also in the surrounding healthy tissues. This can lead to short and long term toxicity and limits the radiation dose that can be given to the tumor. Since the DNA repair capacity of healthy cells is usually more efficient than that of malignant cells, the radiation treatment is fractionated over a number of daily treatments to maximize the effect of the radiation to the tumor while minimizing the damage to healthy cells. Higher dose (in principle) leads to a better tumor control probability (TCP), but with the added risk of a higher normal tissue complication probability (NTCP).

Both the TCP and the NTCP follow sigmoid curves (Fig. 1.2) with respect to the radiation dose (higher dose results in higher probabilities). The difference between the two curves determines the therapeutic window and this can be used to determine the prescription dose. Reducing the dose to the surrounding normal tissues while maintaining or increasing the dose to the tumor can be achieved by creating highly conformal dose distributions with very steep dose gradients around the target volume.

Creating these “ideal” dose distributions requires the complete treatment chain in radiotherapy to be optimal. First, the location of the tumor must be known with great precision. To enable this, a computed tomography (CT) scan is made of the patient and used to define the location of the tumor (section 1.2.2), sometimes in combination with a magnetic resonance imaging (MRI) scan. Next, the dose must be delivered using a technique that allows for fast and accurate modulations of the
radiation beams to achieve the desired, conformal, dose distributions (section 1.2.3). Last, the dose must be delivered at the correct location, therefore the position of the target volume relative to the treatment machine must be known with great precision. Image guided radiotherapy (IGRT) plays a crucial role in this last part of the chain and will be discussed more in section 1.2.4.

Target definition, geometric uncertainties and treatment margins

The target volume (e.g. tumor, its suspected microscopic extensions and surrounding affected lymph nodes) is defined by a physician using a pre-treatment CT scan. First, the macroscopically visible gross tumor volume (GTV) is identified and delineated on the CT. Next, this GTV is expanded by a margin to include surrounding microscopic tumor growth, yielding the clinical target volume (CTV). Last, the geometric uncertainties are combined in an additional margin that is used to expand the CTV resulting in the planning target volume (PTV) [17–19].

A distinction is made between the systematic and random components of the geometric uncertainties (i.e. errors). Systematic errors typically originate in the treatment preparation phase and therefore have the same effect on all treatment fractions [20]. Random errors have a different effect every time and therefore typically result in a blurring of the dose distribution with respect to the tumor [20].

The errors are determined for patient groups and the obtained findings are then used to determine the PTV margin (i.e. population based margins). The PTV margin ($M$) is given by: $M=2.5\Sigma+0.7\sigma$. Where $\Sigma$ is de root mean square of the systematic components of all errors that can occur in a treatment and $\sigma$ is the root mean square of the random components [20–23]. This "margin
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The "recipe" is based on the constraint that at least 90% of all patient should have a minimum dose to the CTV of at least 95% of the prescribed dose.

Radiation delivery techniques

This thesis will focus on external beam radiotherapy (EBRT), where an external radiation source is used to irradiate the target using high energy (MV) radiation consisting of either photons or charged particles. Mostly, linear accelerators (linac) are used. The linac generates the photon beam by directing accelerated electrons towards a Tungsten target where in turn the photons are generated [24].

After generation of the photon beam, modulation of the beam shape is performed by a system of collimators. First, the general size and location of the radiation field is determined using the primary collimator blocks inside the treatment head of the linac. Next, a multileaf collimator (MLC) is used to shape the field further to generate field segments that can be highly conformal to specific anatomical structures (Fig. 1.3). A modern MLC consists of 160 leaves that can all move independently from each other and have a projected field size of 5 mm at the isocenter [25,26]. The MLC can conform the beam to the target volume, but can also be used to create smaller (partial) fields so that after consecutive delivery of these field segments, a specific dose profile can be achieved.

Irradiating a patient using EBRT can be done using different techniques. One of the more straightforward approaches is using a 3-dimensional conformal radiotherapy (3DCRT) technique. With this technique, the patient is irradiated with multiple beams from fixed angles and the MLC is used to conform each field to the target volume seen from that respective angle [27]. The dose to the surrounding healthy tissues within the path of the beams can be relatively high, but this depends on the number of beams in the treatment plan (i.e. more beams means on average a lower dose to healthy tissues).

Intensity modulated radiotherapy (IMRT) is a more sophisticated irradiation technique [28]. In IMRT the patient is irradiated with multiple beams from fixed angles, but each beam now consists of a combined number of segments with different field shapes that, when combined, generate an intensity...
profile. Such a profile can be used to create dose distributions with steeper dose gradients and better sparing of healthy tissues.

Modern linacs also allow for continuous irradiation of a patient while the gantry is rotating around the patient. This is known as volumetric modulated arc therapy (VMAT) [29], the rotational variant of IMRT. During the rotation around the patient the shape of the radiation field and intensity of the beam are continuously modulated. Both IMRT and VMAT have been identified as being superior compared with conformal irradiation techniques when it comes to pancreatic cancer [30].

**Image guided radiotherapy**

The most important recent change in radiotherapy was the introduction of online position verification of the patient. This was made possible by using imaging systems mounted on the linac, leading to the image guided radiotherapy (IGRT).

Early on, imaging on the linac was done using an electronic portal imaging device (EPID) [31–33]. The EPID consists of a detector mounted opposite of the treatment head and this detector is therefore able to measure the intensity of the incoming MV radiation of the treatment beam (Fig. 1.4). This enabled imaging of the patient during irradiation. This type of imaging typically allows for visualization of regions with high contrast such as the bony anatomy, the lungs or even some types of tumors. This can be used to correct for small misalignments. Tumors with a low contrast and that do not have a fixed position relative to the bony anatomy can still be misaligned relative to the beam.

![Fig. 1.4: ELEKTA Agility™ linear accelerator with electronic portal imaging device (EPID) and cone-beam CT (CBCT) imaging system.](image-url)
In 2002 a new imaging system was introduced to perform volumetric imaging of the patient while lying on the treatment table [34]. This cone-beam CT (CBCT) system consists of an X-ray tube and a detector and the system is mounted on the linac so that the treatment beam axis and the CBCT beam axis are perpendicular (Fig. 1.4). The CBCT system can image the patient while the system is rotating around the patient, and by using a back-projection reconstruction algorithm a volumetric image of the patient can be obtained. This image can then be registered to the planning CT of the patient based on the bony anatomy and based on the soft tissues and this leads to a more accurate positioning of the patient compared with using an EPID [35].

Even though the CBCT system yields better soft tissue contrast, target visualization is only possible with high contrast of the target with respect to its surroundings (such as with lung tumors). However, for most treatments the contrast is not sufficient to distinguish the tumor. In this case, the positioning of the patient cannot be based on the exact tumor location. A solution for this problem was presented with the introduction of intratumoral fiducials that give a high contrast on CT and CBCT. These fiducials are typically coiled or ribbed to avoid migration after implantation. The fiducials can be implanted using an ultrasound-guided endoscopic procedure in combination with a thin needle [36]. The fiducials are clearly visible on CT and CBCT images and since it has been shown that these fiducials do not migrate during the course of radiotherapy they can be used as surrogates to determine the tumor position [37,38]. An example of the possible difference between image registration based on bony anatomy and based on intratumoral gold fiducials is shown in Fig. 1.5.

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**Fig. 1.5:** Transverse CT slice of a pancreatic cancer patient (a) and a transverse cone-beam CT (CBCT) slice of the same patient (b). The implanted intratumoral gold fiducials are indicated by the red arrow. Image registration between the CT (purple) and cone-beam CT (CBCT; green) image can be performed based on the bony anatomy (c) or based on the fiducials (d). Regions with a good match after the registration become white. There is a clear mismatch between the fiducial locations on CT and CBCT when image registration is performed based on the bony anatomy.
Respiratory motion management

In addition to daily tumor position variations, a major geometric uncertainty arises from the tumor motion during irradiation, the intrafractional motion. This motion is predominantly the result of cardiac, gastrointestinal and respiratory-induced motion [39,40]. Intrafractional motion typically results in a blurring of the dose distributions and can therefore result in a decrease in dose to the target [41,42]. We will focus on the respiratory motion from now on since this is the most dominant cause of the intrafractional uncertainty.

Upper abdominal tumors undergo respiratory-induced motion as these tumors are often in close proximity to the diaphragm. These tumors, amongst others, include: liver-, pancreatic-, stomach- and kidney tumors. Respiratory-induced motion is more prominent for some tumor sites than for others. The extent of the motion can be different for each patient and depends on tumor size, location and whether the tumor is attached to other structures. Several techniques are available to perform respiratory tumor motion management [43–51].

Respiratory-induced tumor motion is often accounted for by using a so-called motion-encompassing technique [50]. Prior to the treatment the magnitude of the respiratory motion is measured using pre-treatment imaging, mostly a 4-dimensional CT (4DCT) scan [52]. With a 4DCT the respiratory cycle, from end-inhalation to end-exhalation, is divided in 10 phases and for each phase there is a CT scan of the patient representing the anatomy during that specific respiratory phase.

The 4DCT can be used to determine the tumor position during the complete respiratory cycle and this can be used to define a volume that encompasses the tumor during this entire cycle. First, the GTV is delineated on each respiratory phase scan. Next, the GTVs are combined into a volume that encompasses the GTV during the complete respiratory cycle which is referred to as the internal-GTV (iGTV). This iGTV is then expanded to create the internal-CTV (iCTV) and subsequently this iCTV is expanded to create the PTV (Fig. 1.6) [53].

**Fig. 1.6:** Transverse slice of a CT of a patient with a pancreatic-head tumor with implanted intratumoral gold fiducials. The colored lines indicate the different target volumes that are used for target definition and treatment planning.
Radiotherapy of pancreatic cancer

Limitations of radiotherapy for pancreatic cancer
The effectiveness of the radiation treatment of pancreatic cancer depends on the prescribed dose. Higher dose may result in better survival rates, but this is still very much under debate [54]. Unfortunately, the tumor is often located in very close proximity to the duodenum and other organs at risk (OARs), limiting the prescription dose. The dosimetric constraints for these OARs have been investigated and reported in a number of studies [55–59].

Using an iGTV, which is considered as a conservative approach [60], to account for the respiratory-induced motion can result in a large PTV. Especially, in combination with the PTV margin that is necessary to account for all other geometric uncertainties such as delineation uncertainties [61,62]. Because for each patient the respiratory-induced motion magnitude is directly used to expand the GTV to create an iGTV, it accounts for a major part of the PTV.

The respiratory-induced motion can show large variations over time, both short- and long-term (short-term variation is illustrated in Fig. 1.7). The long-term variation often comes in the form of a drift of the mean tumor position. However, it is often not taken into consideration that the used motion magnitude is based on a single snapshot in time and that the motion measured on this single pre-treatment 4DCT might not be representative for the motion during the rest of the treatment [63,64].

Respiratory-induced pancreatic motion
A number of studies quantified the respiratory-induced motion of the pancreatic head and tumor in patient and healthy subject groups, the observed magnitudes in all three directions are given in Table 1.1 [42,63–77]. There is a substantial variation in the reported respiratory-induced motion magnitudes, which can partially be explained by the fact that these results were obtained under varying circumstances and using multiple different imaging modalities. The results do indicate that it can be challenging to capture the respiratory motion for this patient group in a single value. Especially

Fig. 1.7: Pancreatic tumor position during a 2-minute cone-beam CT acquisition illustrating the respiratory-induced tumor motion and the short-term variation in this motion.
when the motion during the actual treatment is larger than during the treatment planning phase, the
target coverage can be degraded due to blurring of the dose [78]. Therefore, good respiratory-induced
motion management is paramount.

Table 1.1: Pancreatic respiratory-induced motion magnitudes in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>IS (mm)</th>
<th>AP (mm)</th>
<th>LR (mm)</th>
<th>Imaging modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bussels et al.</td>
<td>21.6</td>
<td>6.0</td>
<td>12.1</td>
<td>MRI</td>
</tr>
<tr>
<td>Gierga et al.</td>
<td>7.4</td>
<td>3.8</td>
<td>NA</td>
<td>Lateral fluoroscopy</td>
</tr>
<tr>
<td>Bhaskin et al.</td>
<td>13.8</td>
<td>NA</td>
<td>3.2</td>
<td>Fluoroscopy</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>11.6</td>
<td>2.7</td>
<td>2.0</td>
<td>4DCT</td>
</tr>
<tr>
<td>Henry et al.</td>
<td>6.6</td>
<td>4.8</td>
<td>&lt;2</td>
<td>MV movies</td>
</tr>
<tr>
<td>Mori et al.</td>
<td>8.9</td>
<td>2.6</td>
<td>1.4</td>
<td>4DCT</td>
</tr>
<tr>
<td>Feng et al.</td>
<td>20.0</td>
<td>7.0</td>
<td>Negligible</td>
<td>MRI</td>
</tr>
<tr>
<td>Gwynne et al.</td>
<td>15.3</td>
<td>9.7</td>
<td>5.2</td>
<td>Breath-hold CT</td>
</tr>
<tr>
<td>Minn et al.</td>
<td>9.2</td>
<td>3.8</td>
<td>3.2</td>
<td>4DCT</td>
</tr>
<tr>
<td>Goldstein et al.</td>
<td>5.2</td>
<td>3.0</td>
<td>3.0</td>
<td>4DCT</td>
</tr>
<tr>
<td>Wysocka et al.</td>
<td>13.1</td>
<td>6.3</td>
<td>2.4</td>
<td>Breath-hold CT</td>
</tr>
<tr>
<td>Huguet et al.</td>
<td>15.0</td>
<td>6.5</td>
<td>4.2</td>
<td>4DCT</td>
</tr>
<tr>
<td>Hallman et al.</td>
<td>5.0</td>
<td>1.6</td>
<td>NA</td>
<td>4DCT</td>
</tr>
<tr>
<td>Shinohara et al.</td>
<td>19.1</td>
<td>7.8</td>
<td>5.3</td>
<td>Implanted transponders</td>
</tr>
<tr>
<td>Whitfield et al.</td>
<td>20.6</td>
<td>10.1</td>
<td>6.7</td>
<td>Fluoroscopy and CBCT</td>
</tr>
<tr>
<td>Ge et al.</td>
<td>16.9</td>
<td>6.9</td>
<td>3.4</td>
<td>4DCT</td>
</tr>
</tbody>
</table>

Abbreviations: IS = inferior-superior; AP = anterior-posterior; LR = left-right; NA = not available; MRI = magnetic resonance imaging; CT = computed tomography; 4DCT = 4-dimensional CT; MV = mega voltage; CBCT = cone-beam CT.

Objective and outline of this thesis

The main objective of this thesis is to describe and optimize new and existing techniques for respiratory-induced pancreatic tumor motion management. These techniques either account for the present respiratory-induced motion or focus on eliminating the respiratory-induced motion.

We will first show in chapter 2 that the daily respiratory-induced motion cannot adequately be described by a single pre-treatment 4DCT measurement. We measured the respiratory-induced motion magnitudes in a group of pancreatic cancer patients using the pre-treatment 4DCT scans as well as all daily CBCT scans. We compared the pre-treatment respiratory-induced motion magnitudes to the daily magnitudes.

In chapter 3 and chapter 4 we will introduce and describe two treatment planning approaches that can be used to account for the respiratory-induced motion of pancreatic tumors. First, we
investigated the mid-ventilation approach. Second, we investigated the use of a probabilistic treatment planning approach.

Breath-holding is often used during treatment instead of allowing the patient to breathe freely, it is assumed to result in a highly stable anatomy. Chapter 5 describes the results of our prospective patient study in which we investigated and quantified the geometric uncertainties when using breath-holding in pancreatic cancer patients.

In chapter 6 we describe a study in which we asked healthy subjects to perform multiple breath-holds with different lung volumes. We investigated the motion of the pancreatic head and of the diaphragm during breath-holding using MRI and we compared this between the different lung volumes in order to determine the ideal lung volume for breath-holding during radiotherapy.

In chapter 7 we will discuss the presented work and its limitations. We will consider the extension of the presented work to other treatment sites and other treatment techniques, and we will discuss alternative solutions for respiratory-induced motion management. We will also address potential future research and techniques.
Chapter 1

References

Introduction


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Introduction