MRI of pancreatic cancer for radiotherapy
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CHAPTER 1

Introduction and outline

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CHAPTER 1

Introduction
In the following paragraphs I will elaborate on the title of this thesis: “Magnetic resonance imaging of pancreatic cancer for radiotherapy”. First, pancreatic cancer and treatments for pancreatic cancer are discussed. Then, radiotherapy of pancreatic cancer patients is explained in detail. Several shortcomings of image guided radiotherapy might be overcome by magnetic resonance imaging (MRI). Therefore, MRI, and in particular diffusion-weighted imaging (DWI), is explained and put into the perspective of radiotherapy. Finally, the outline of this thesis is discussed, in which MRI techniques are developed, optimized and validated for radiotherapy of pancreatic cancer patients.

Pancreatic cancer
Pancreatic cancer is one of the deadliest of all major cancers with a median survival of 4.4 months after diagnosis [1]. Pancreatic cancer often (78%) occurs in the head of the pancreas (Fig. 1.1 illustrates pancreatic anatomy), but also can occur in the body (11%) or tail (11%) [2]. The estimated number of mortalities as a result of pancreatic cancer worldwide (330,400 per year) is only marginally smaller than the estimated incidence (337,900 per year) [3]. Therefore, pancreatic cancer is currently ranked as the fourth most common cause of cancer-related deaths in more developed countries, whereas it is only the tenth most common cancer. Despite all technical advances in medicine, the survival rate of pancreatic cancer has not largely improved in the past 30 years [4]. Pancreatic cancer is therefore expected to soon become the third most common cause of cancer-related deaths [5].

The only known potentially curative treatment for pancreatic cancer is surgical resection [6]. Only tumors that do not involve the celiac artery or superior mesenteric artery and show no distant metastases are eligible for resection [7, 8]. Therefore, unfortunately, only 15–20% of pancreatic cancer patients are eligible for surgery at the time of diagnosis [9]. Furthermore, even after a successful resection with no remaining tumor at the edge of the resected specimen, patients still have a poor median survival of 23 months [10].

In addition, chemotherapy, radiotherapy and radiochemotherapy (i.e. the combination of radiotherapy and chemotherapy) are commonly applied. These therapies are used in a palliative setting [11, 12] or alongside surgery to improve tumor control. When these therapies are used alongside surgery, it is either in an adjuvant (after surgery) [13-16] or neoadjuvant (before surgery) [17-21] setting. Despite the indication that (neo)adjuvant radiochemotherapy may improve pancreatic cancer
patients life expectancy [15, 21], may delay recurrent disease [16] and may improve local tumor control [19], there are still many challenges in radiotherapy that should be overcome to improve the treatment outcome further.

Radiotherapy
In radiotherapy, ionizing radiation is used to kill cancer cells. The ionizing radiation can damage DNA in cells, which can cause cell death. Pancreatic cancer patients are typically irradiated by an ionizing beam that originates in a linear accelerator (linac, Fig. 1.2). In such a setup, the radiation penetrates the patient to reach the tumor. Therefore, healthy tissue is inevitably irradiated too. DNA of both tumor and healthy tissue can be damaged from the ionizing radiation. However, healthy tissue repairs the DNA damage more rapidly than tumor tissue. Therefore, radiotherapy is usually administered in multiple daily fractions, whereby the healthy tissue recovers more than the tumorous tissue between each session. Due to the toxicity of irradiation, the goal of radiotherapy is to maximize the dose to the tumor while minimizing the dose to healthy tissue, in particular, radiation sensitive organs at risk (OARs). For pancreatic cancer patients, the OARs include the small bowel, stomach, liver, kidneys and spinal cord.

![Figure 1.1. Magnetic resonance images (left: T1-weighted, right: T2-weighted) of the pancreas of a healthy volunteer. The pancreas (dotted lines), including the pancreatic head (h), body (b) and tail (t), the liver (†), the kidneys (#), and the stomach (†) are accentuated.](image)
Treatment planning

In order to maximize the dose to the tumor while sparing OARs, it is necessary to image these structures. Therefore, before the start of therapy, computed tomography (CT) images are obtained (Figs. 1.3 and 1.4 a), called a planning CT. A radiation oncologist then delineates the visible tumor and lymph nodes with potential tumor cells on all the image slices of the planning CT. This delineated volume is known as gross tumor volume (GTV; Figs. 1.3 a and c). As microscopic extensions of the tumor may not be visible on the CT images [22], the GTV is expanded by a margin, typically of several millimeters, to generate a clinical treatment volume (CTV). The CTV includes these suspected microscopic extensions. As irradiation often lasts several minutes per session, patients are mostly irradiated during free breathing. To include the CTV during the full respiratory cycle, an additional margin is added to the CTV to generate the internal target volume (ITV). A CTV-ITV margin that incorporates all motion for every patient will overestimate the motion for most individual patients as respiratory motion varies between subjects [23]. Therefore, patient specific margins can be determined instead, using inhalation and exhalation breath-hold CT [24],

Figure1.2. A photo of a linac. The patient is located at the center of the beam. The linear accelerator gantry (*) from which the radiation beam emerges is able to rotate around the patient (arrow) together with the cone beam computed tomography device (#).
4DCT [25] or MRI images [26, 27]. Finally, to deal with all other uncertainties, such as patient setup errors and errors in the original GTV delineation, an additional margin (typically 10–15 mm) is added to the ITV to generate a planning target volume (PTV) [28]. In radiotherapy planning the aim is to develop a plan that irradiates the PTV at a high dose, while minimizing the dose to the OARs. For this reason, the OARs are also delineated on the planning CT.

After generating the PTV and delineating the OARs, a treatment plan is designed. In such a treatment plan, beam settings are optimized such that the predefined required dose to the PTV (tumor) is reached while OARs have an as low dose as possible (Figs. 1.3 b and d). In modern radiotherapy, the angle under which the patient is irradiated can be varied by rotating the beam around the patient. Furthermore, the shape and intensity of the beam can be modulated during treatment. By doing so, very steep dose gradients between the PTV and OARs can be achieved. This is done either using several predefined angles and beam shapes (intensity modulated radiotherapy; IMRT) [29] or a continuously changing beam shape that rotates around the patient (volumetric modulated arc therapy; VMAT) [30].

**Treatment**

Typically, radiotherapy of pancreatic cancer patients is fractionated over multiple (15–28) daily sessions [31]. During each session, the target volume (i.e. PTV) should be aligned with the radiation beam of the linac to ensure that the planned treatment is delivered accurately. Most linacs contain an integrated cone beam CT (CBCT) device (Fig. 1.2) which allows making 3D volumetric CT-like images of the patient’s anatomy while on the treatment couch (Fig. 1.4 b) [32]. Such a CBCT allows determining the shift of the patient’s anatomy as presented on the treatment couch compared to the anatomy on the planning CT. The patient’s treatment couch can then be moved according to the found shift between both scans to ensure alignment of the PTV with the treatment plan.

Determining the shift between the CT and CBCT is done with respect to some anatomical landmarks visible both on the planning CT and CBCT. As the CBCT has poor soft tissue (e.g., pancreas) contrast, but good contrast of bones, often the bony anatomy was used as landmarks. However, the position of the PTV with respect to the bony anatomy can change between the planning CT and daily CBCT as a result of e.g., bowel filling [33]. Therefore, nowadays small (sub-mm diameter) golden fiducial markers that are visible on CT and CBCT (Fig. 1.4 a-b) are placed endoscopically with thin needles (inner diameter of approximately 0.4 mm) inside the tumor in some clinics.
These markers are then used to match the planning CT and CBCT images and ensure alignment of the PTV [33, 37-39].

Finally, respiratory motion during radiotherapy effectively results in blurring of the dose [40]. If ignored, this motion can lead to under treatment of the tumor and additional radiation to OARs. Classically, the respiratory motion is included in the PTV by introducing an ITV, as mentioned above. Including the uncertainties due to respiratory motion results in larger PTVs and hence may cause higher dose to OARs. Therefore, there are several alternative approaches to address the respiratory motion. For example, patients can be treated in mid-ventilation [41] or during breath-holding [42, 43]. Also, gating or tracking techniques may be used [44-46]. These techniques can potentially eliminate the use of an ITV and hence decrease the size of the PTV, reducing toxicity.

![Delineated GTV (yellow), CTV (blue), ITV (orange) and PTV (red) volumes, as well as some OARs (liver + kidneys; green) projected on a planning CT scan in axial (a) and coronal (c) view. Treatment plans based on these delineated volumes are presented too (b, d).](image)

Figure 1.3. Delineated GTV (yellow), CTV (blue), ITV (orange) and PTV (red) volumes, as well as some OARs (liver + kidneys; green) projected on a planning CT scan in axial (a) and coronal (c) view. Treatment plans based on these delineated volumes are presented too (b, d).
There is further room for improvement in radiotherapy of pancreatic cancer patients. Currently, there is a large variation between observers in GTV delineation (i.e. a poor interobserver agreement) [47-49]. As the entire treatment is based on the delineated GTV, any error in this delineation impacts the entire treatment. Therefore, GTV delineations should be as accurate as possible. These delineations are currently often based on CT images, which have poor soft tissue contrast and hence poor pancreatic tissue and tumorous tissue contrast (Fig. 1.4 a-b). Potentially scans with better soft tissue contrast may improve the accuracy of the GTV delineation. Furthermore, some patients have pancreatic cancers that are unresponsive to radiotherapy. For these patients, radiotherapy is undesirable as the irradiation will only damage healthy tissue. As discussed further on, both issues can potentially be addressed by MRI.

Figure 1.4. CT (a), CBCT (b) and MRI (c-d) images of a pancreatic cancer patient. The biliary stent (arrow) and fiducial markers in the pancreatic tumor (arrowhead, not visible in MRI images) are accentuated.
Magnetic resonance imaging

MRI is a medical imaging technique that allows for imaging patient’s anatomy. MRI manipulates proton spins of specific atoms (typically hydrogen) using strong magnetic fields (typically 1.5 T to 3 T) and a sequence of radiofrequency pulses and magnetic field gradients, called pulse sequence, to generate images [50]. By varying settings of the pulse sequence, different types of contrasts can be achieved, such as T1- or T2-weighted contrasts (e.g., Fig. 1.5 a-b). Furthermore, MRI can be used to quantify specific tissue properties, such as the T1-values [51], T2-values [52, 53], diffusivity [54] and the amount of perfusion [55, 56] of tissue. In such a case, maps are created of these specific tissue properties (e.g., Fig. 1.5 d-f).

In this thesis we focus on the following sequences: T1-weighted, contrast enhanced (CE) T1-weighted, T2-weighted, and DWI images (Fig. 1.5). T1-weighted images of the pancreas can be obtained in a single breath-hold at high resolution [57]. However, most tumors, are poorly visible on plain T1-weighted images and therefore the acquisition is repeated after an intravenous gadolinium contrast injection to generate CE images. As pancreatic tumors are often poorly perfused, the contrast medium will initially mainly enhance the signal from healthy tissue, resulting in hypo intenser (i.e. darker) tumor tissue compared to surrounding more enhanced healthy tissue in such CE images (Fig. 1.5 c). T2-weighted images often have high in-plane resolutions, but poor through-plane resolution [57]. Furthermore, T2-weighted images are often acquired during several breath-holds, which can result in a mismatch of anatomy between neighboring slices. T2-weighted images have good soft tissue contrast for OARs. Moreover, T2-weighted images offer complimentary information to T1-weighted images which can help in differentiating between tumor, necrosis and inflammation.

Diffusion-weighted imaging

In DWI, gradients in the magnetic field (called diffusion gradients) are applied before signal read-out to sensitize the MRI signal to the diffusion of water molecules. Diffusion is the intermingling of molecules as a result of random motion of the molecules due to their kinetic energy. DWI uses the diffusion of hydrogen molecules to generate contrast in images. In DWI, images with different diffusion weightings are acquired, which is achieved by varying the diffusion gradients’ strength. A 4D data set is then created, in which the signal is described as function of diffusion weighting for the three spatial dimensions. For each voxel in the spatial dimensions, a diffusion model can be fitted to the signal as function of diffusion weighting. In the classical diffusion model, the signal attenuation as a function of diffusion weighting is modeled
INTRODUCTION AND OUTLINE

monoexponentially. The model parameter apparent diffusion coefficient (ADC) is then found by fitting this monoexponential DWI model. When such a monoexponential fit is made for each voxel, an ADC-map can be generated (Fig. 1.5 d). ADC represents the diffusivity of water in tissue. The ADC depends on the microscopic structure of tissue and often gives good contrast between pancreatic tumors and healthy tissue [58-61].

However, many competing models describe DWI data. The most well-known competing model is the intravoxel incoherent motion (IVIM) model (Fig. 1.5 e-f). In the IVIM model, the sensitivity of DWI-signal to perfusion effects is modeled as well. Perfusion is the flow of blood through tissue. In this model, the signal from blood in capillaries dephases more rapidly as a function of diffusion weighting than signal from tissue. To model both components, the IVIM model assumes DWI data decays bi-exponentially as a function of diffusion weighting. Since the introduction of the IVIM model, the non-monoexponential behavior of DWI data in the pancreas was confirmed in multiple studies [60-65] and related to perfusion [66, 67]. The added perfusion parameters of the IVIM model have shown additional value for lesion characterization in the pancreas [60-65] and enabled treatment response monitoring in various other organs [68, 69].

DWI is often limited to poor resolutions and acquisition times of several minutes. Therefore, DWI is either imaged during free breathing [70, 71], in multiple breath-holds [62] or during respiratory gating/triggering [72].

MRI and radiotherapy

In this thesis two potential applications of MRI for radiotherapy are discussed: MRI during treatment planning and MRI for monitoring treatment response. For several organs, it was shown that when MRI, which has good soft tissue contrast (Fig. 1.5 c-d) [57, 73-75], is added during treatment planning, delineations improved [76-79]. Therefore, MRI may also improve tumor delineation for pancreatic cancer patients. Andreychenko et al. [80] suggested that the most useful MRI images for target volume delineation of pancreatic cancer patients would be T1-weighted, contrast enhanced (CE), T2-weighted, and DWI images (Fig. 1.5 a-d). Whether GTV delineation is improved with MRI has not been investigated for pancreatic cancer patients.

Furthermore, some tumors are insensitive to irradiation, so-called radioresistant tumors. If the lack of treatment response could be detected at an early stage of treatment (known as treatment response monitoring), or, ultimately, if tumor sensitivity to irradiation can be determined before treatment, unnecessary irradiation can be prevented. There are several promising MRI pulse sequences that may be able
to monitor the response of the tumor to treatment or determine the tumor sensitivity to irradiation before treatment. Part of this thesis focusses on one of these pulse sequences, namely DWI and in particular the IVIM model for DWI. It is known that low diffusivity in the tumor before treatment is related to poor treatment outcome in both chemotherapy [81] and radiochemotherapy [82] of the pancreas. It was suggested that low perfusion before treatment of several therapies may also relate to limited treatment response [83]. Therefore, IVIM modeling of DWI may prove a useful tool for treatment response monitoring and treatment outcome prediction in the pancreas.

![Figure 1.5](image)

**Figure 1.5.** Six different MRI images of the same patient. Images include standard non-CE (a, b), CE T1-weighted (c) and DWI (d-f) images. Diffusion maps obtained from different fit models (d, e) and a perfusion fraction map (f) are displayed. The white ellipse surrounds the tumor.
Outline of this thesis

In this thesis, MRI techniques are optimized for the purpose of radiotherapy of pancreatic cancer patients, and the added value of MRI is assessed.

First, in chapter 2 the interobserver variation of tumor delineation on CT images is quantified to assess the current clinical practice as a baseline. Then, in chapter 3, the value of offering MRI images alongside the CT images for delineating pancreatic cancers is quantified.

When MRI is offered alongside CT, it is desirable that the images are matched, which is best done using intratumoral fiducial markers [33, 37]. Therefore, in chapter 4 the visibility and artifacts caused by fiducial markers on MRI images are quantified using a pulse sequence-independent approach. As 70% of the pancreatic cancer patients receive biliary stents, which are often located close to the tumor, the same approach is used to quantify artifacts caused by biliary stents in chapter 5.

During radiotherapy, tumors are treated with high precision and hence 3D high-resolution imaging is desired. A disadvantage of common T2-weighted pulse sequences is its thick slices. Therefore, in chapter 6, an alternative T2-weighted-like pulse sequence that allows for high 3D resolution is optimized for imaging of the pancreas.

In chapter 7 the acquisition of DWI for IVIM model fitting in the pancreas and liver is optimized. In chapter 8 the fit algorithm for the IVIM model is optimized, and the IVIM model is compared to other DWI data models considering pancreatic tumor contrast, treatment monitoring, and treatment outcome prediction.

Finally, in chapter 9 the findings of this thesis are set in clinical perspective and the future of MRI for pancreatic radiotherapy is discussed.
References


INTRODUCTION AND OUTLINE


