Quantitative imaging to characterize pancreatic and esophagogastric cancer

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Chapter 1

Introduction & Outline

Introduction

The pancreas, esophagus and stomach are part of the foregut, which originates from the endoderm during embryotic development. Together with the hepatobiliary system and duodenum they form the upper gastro-intestinal tract, responsible for the first phase in the digestion and extraction of nutrients from the food we eat. Furthermore, the exocrine function of the pancreas plays an important role in blood glucose level regulation. External factors and genetic predisposition can cause mutations of normal cells and when regulatory processes are no longer able to control cell growth and proliferation, neoplasms can form. This process is commonly known as cancer. The formation of neoplasms can lead to a loss of normal organ function and related symptoms, ultimately leading to death. In general, cancers originating from the pancreas, esophagus and stomach are diagnosed in a late stage of the disease due to the late presentation of symptoms. Since treatment is most effective in early stage disease, overall survival is generally limited. When treatment is given, a great variety in the efficacy of treatments between patients is observed. Unfortunately there is a lack of clinical markers that can identify which treatment will be effective before or early after treatment has started. Therefore, most patients are treated with the same therapy based on cancer type, stage and clinical condition. Efficacy of treatment is evaluated by tumor size criteria measured on computed tomography (CT) imaging and is generally performed after several months of treatment [1]. As a result, some patients are treated with ineffective therapy for too long, only experiencing the negative (side) effects of that treatment.

In order to tailor treatment, there is a great clinical demand for (non-invasive) methods that can predict or identify treatment response in an early stage and provide further insights in the biological processes involved in the progression of the disease. Quantitative imaging techniques may provide such methods and aim to model imaging data into quantitative values representing specific characteristics of the underlying tissue [2, 3]. Ideally the resulting parameters give an objective measure of the investigated characteristic, independent of external factors. In theory, such parameters could enable treatment response evaluation by monitoring parameter changes, reflecting biological therapy effects, over time or predict treatment outcome before it has commenced.

In this introduction the background of pancreatic and esophagogastric cancer will be further elaborated on. Furthermore, the basis of several quantitative imaging methods will be described and how these techniques could potentially be utilized to address the demand for biological and prognostic markers in the clinical work-up of these cancers.

Pancreatic cancer

Acinar-to-ductal metaplasia (ADM), the process where pancreatic acinar cells differentiate into ductal cells, is a common process in the pancreas. However, under the influence of genetic defects or environmental stress it can lead to neoplasia. This most common form of pancreatic cancer, arising from intraepithelial neoplasia of the pancreatic ducts, is pathologically classified as ductal adenocarcinoma. Pancreatic ductal adenocarcinoma (PDAC) ranked 4th on the list of cancer related deaths in 2018 [4] and is predicted to rank 2nd by 2030 in the USA [5]. Patients typically present with jaundice, abdominal pain, poor appetite, weight loss, nausea, vomiting, and often type 2 diabetes [6]. Contrast enhanced CT is the primary diagnostic tool for both the diagnosis, staging and follow-up of pancreatic cancer [7]. Endoscopic ultrasound can be performed when lesions are conspicuous on CT, with the benefit that fine needle aspirations with cytological evaluation can be performed. When there is a high suspicion of liver or other metastasis on the CT scan, often ultrasound guided biopsies are performed to rule out lesions of other origin.

Only a small portion of the patients (15-20%) present with, curable, surgically resectable disease [8]. Local resectability is based on CT determined disease involvement of the superior mesenteric artery, celiac axis, common hepatic artery, mesenteric and portal vein (Table 1.1). Resection is considered when involvement of these structures is limited and tumor free resection margins can be achieved (R0 resection). In the Netherlands, median survival after resection is still limited with just over 1 year [9, 10].

Table 1.1 Dutch Pancreatic Cancer group definition of local resectability of pancreatic adenocarcinoma [11]

	SMA	Celiac axis	CHA	SMV-PV
Resectable (all four required)	no contact	no contact	no contact	⩽90° contact
Borderline resectable (minimally one required)	⩽90° contact	⩽90° contact	⩽90° contact	90°-270° contact & no occlusion
Irresectable (minimally one required)	>90° contact	>90° contact	>90° contact	>270° contact or occlusion

SMA superior mesenteric artery, CHA common hepatic artery, SMV superior mesenteric vein, PV portal vein

The group of patients that present with resectable, but already limited locally advanced disease is often referred to as borderline resectable (Table 1.1). To improve outcome of this patient group, treatment regimens involving (neo-adjuvant) chemotherapy, radiotherapy or a combination of the two have been proposed [12]. The rationale behind these treatments is to induce local response before resection and treat micro-

metastases before they manifest. Selection of patients for these treatments is difficult. Results from trials incorporating neo-adjuvant treatment have shown mixed outcomes [13] and there are no known factors that can indicate a response to treatment forehand.

The majority of the patients however present with either irresectable locally advanced (35%) or metastatic (50%) disease [14]. Surgical treatment of locally advanced disease, leaving macroscopic tumor margins around important anatomical structures (R2-resection), results in similar outcome as no resection [15]. Patients with locally advanced diseased are therefore generally considered incurable and treated in the same way as patients with metastatic disease. Treatment of these patients most commonly involves either gemcitabine based (whether or not in combination with capecitabine or nab-paclitaxel) [16, 17] or FOLFIRINOX (leucovorin and fluorouracil combined with irinotecan and oxaliplatin) [18] chemotherapy to extend life or improve its quality. Although these treatment regimens in general do increase overall survival, efficacy varies greatly between patients and overall survival remains limited with a median of just 6-11 months.

Esophageal & Gastric Cancer

The esophagus and stomach together form the first part of the digestive system. Esophageal cancer can be divided in two main entities, originating from two different cell types; the squamous cell carcinomas and the adenocarcinomas [19]. Squamous cell carcinomas are more prone to form in the proximal part of the esophagus under the influence of external factors as alcohol intake and smoking [20]. Esophageal adenocarcinomas are more often formed in the distal part of the esophagus and can be preceded by Barrett's esophagus where acid reflux from the stomach damages the epithelial lining of the esophagus [21]. Gastric cancers are almost always adenocarcinomas. The biggest risk factors to form gastric adenocarcinoma are infections from Helicobacter pylori or the Epstein-Barr virus and smoking [22].

In general, the outcome of both esophageal and gastric cancer is poor, with an overall 5-year survival rate of 10% worldwide [23, 24]. For most patients the development of the disease is asymptomatic, most commonly presenting with dysphagia or indigestion in a later stage of the disease. As a result, only approximately 30% of the patients are diagnosed with regional, curable, disease [25]. Similar to pancreatic cancer, the primary diagnostic tool for the diagnosis, staging and follow-up of esophageal cancer is contrast enhanced CT imaging [19]. Although endoscopy and endoscopic ultrasound also play a key role in determining local boundaries of the esophageal or gastric lesion and targeting of suspected lymph nodes for biopsy. Suspicion of liver or other metastasis on the CT scan is often confirmed by ultrasound guided biopsies.

In resectable esophageal cancer, outcome can be improved by multimodality treatment [26]. The current standard treatment of resectable esophageal cancer consists of neo-adjuvant chemoradiation followed by resection. In the Netherlands, the preferred chemoradiation regimen consists of carboplatin plus paclitaxel with concurrent radiotherapy in 23 fractions of 1.8 Gray targeted on the primary tumor [27]. An FDG PET/CT scan is often performed when neo-adjuvant therapy is considered and after completion of the neo-adjuvant treatment to rule out distant metastasis.

In patients presenting with metastatic disease curative treatment is no longer feasible, resulting in an even dismal prognosis with a median survival of less than a year [28–30]. Standard treatment for these patients consists of chemotherapy with a combination of capecitabine and oxaliplatin (CAPOX) [31, 32]. Because of their overlap in dysregulation of oncogenic pathways, patients with metastatic adenocarcinoma of the esophagus and stomach are often studied collectively and referred to as esophagogastric cancer patients [33].

Tumor microenvironment

Solid tumors, as pancreatic and esophageal cancer, do not solely consist of cancer cells. The microenvironment of the tumor is characterized by a desmoplastic transformation involving severe fibrosis, high levels of immune cell infiltration and hypovascularization often referred to as stroma. A large part of the tumor volume consists of this stroma, surrounding the actual tumor cells [34].

Cancer associated fibroblasts (CAF) play a key role in the formation of the tumor microenvironment. They have been found to harbor tumor promoting activities and exert an extensive mechanical influence on the stroma [35, 36]. By the activation of the CAFs, large amounts of fibrosis and extra cellular matrix consisting of, amongst others, collagen fibers are deposited. Another important step in the development of pancreatic cancer is the activation of pancreatic stellate cells (PSC). These PSC are activated by the tumor cells or the inflammatory response of the pancreatic cells to ductal obstruction caused by tumor growth. When activated PSCs undergo morphological changes, transforming into an activated myofibroblast-like cell. On activation, PSC demonstrate increased expression of α Smooth Muscle Actin (α-SMA) and formation of collagen, contributing to the extracellular matrix of the pancreatic tumor [37]. The activation of PSCs, CAFs and the extent of the extra cellular component varies greatly between patients and has been associated with patient outcome [38–40].

The formation of blood vessels, or angiogenesis, can be upregulated in malignancies to suffice in the demand for nutrients and oxygen. However, since this process is less well-regulated compared to normal vascular formation, the resulting vascular bed is highly abnormal. Vessels are leaky, dilated or constricted and form interconnections in

inefficient ways [41]. As a result, the formed vasculature is far less efficient in providing nutrients and oxygen to the surrounding tissue. This, in combination with the increased interstitial pressure induced by dense fibrosis, make that the tumor microenvironment can become hypoxic [42]. In this hypoxic environment, cancer cells can undergo epithelial-to-mesenchymal transition, demonstrate a more aggressive phenotype and becoming more prone to migrate and form metastasis [43]. Furthermore, radiation therapy is less effective in hypoxic areas due to a lack of oxygen free radical formation [44] and tumor cells located further away from blood vessels are less effected by chemotherapy due to a longer diffusion distance of the therapeutic agent [45]. Tumor hypoxia has therefore been associated with rapid progression, increased metastatic potential, therapy resistance and as a result dismal prognosis in both pancreatic and esophageal cancer [46–50].

The composition of the tumor microenvironment has been associated with tumor progression, treatment resistance and patient outcome. Understanding the tumor-promoting properties would potentially allow for targeted therapies and better patient stratification for treatment [51]. However, characterization of the key features describing the tumor microenvironment is difficult in patients. Often only small tissue samples are available after invasive procedures involving (endoscopic) ultrasound or CT guided biopsies that do not reflect the properties of the tumor in its entirety [52]. Furthermore, longitudinal measurements of these characteristics and monitoring of possible treatment induced changes would involve repeated interventions with high patient burden as one of the costs. To enable for tailor treatment, there is therefore a great clinical demand for non-invasive markers describing the entire tumor, including its microenvironmental properties.

Imaging techniques

In this thesis several quantitative imaging techniques are investigated in the context of pancreatic and esophageal cancer characterization, treatment evaluation and response prediction. In the following sections these techniques will be further elaborated on.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) exploits the ability to manipulate proton spins in a magnetic field to generate images. Using a strong magnetic field of typically 1.5 – 3 Tesla, proton spins can be synchronized. Magnetic gradients and radiofrequency pulses can then be applied to manipulate the spins and generate images. Different settings for gradients and pulses can be used in a pulse sequence to generate different image contrasts.

Thus far the role of MRI is limited in the diagnostic work-up of pancreatic and esophageal cancer, offering limited advantages over CT imaging [7, 53]. If MRI is utilized in the clinical work-up, typically only T1-weighted, after contrast injection, and T2-weighted images are acquired for anatomical localization of lesions. However, by applying different acquisition techniques, MRI has the ability to quantify complex tissue properties.

Dynamic Contrast Enhanced MRI

With dynamic contrast enhanced (DCE) MRI T1-weighted images are continuously acquired during and after the intra-venous injection of a contrast agent. Most used MRI contrast agents are gadolinium-based complexes, where the gadolinium alters the T1-relaxation of the tissue. This change in T1 over time can be measured and, when compared to the baseline T1 of the tissue, quantified in tissue uptake curves. Kinetic modelling can be used to retrieve the underlying tissue properties from these uptake curves. The most used model to quantify DCE data is the Tofts model [54]. In this model the rate of exchange (k_{ep}) of contrast from the vascular compartment to the extracellular extravascular space (v_e) is modelled along with the volume transfer constant (K^{trans}). An additional parameter v_p can be added to model the tissue vascular compartment. DCE MRI has been broadly applied to characterize tumor vascularization [55–59] and to monitor effects of treatment in PDAC [60]. Furthermore, it has shown potential in esophageal cancer response prediction to neo-adjuvant chemoradiotherapy [61].

A more advanced approach to DCE MRI is multi-contrast DCE MRI. In this approach multiple contrast injections are given consecutively during the same acquisition, each with another sized contrast agent. The size of each contrast agent determines its ability to diffuse out of the blood vessel into the interstitial space. By fitting a single model to the combined contrast uptake curve, this approach can give additional information on vascular permeability and blood volume [62]. Multi-contrast DCE has been employed to give insights into the effects of anti-vascular treatment on tumor vasculature and permeability [63]. Given that most of the macro-molecular contrast agents are not clinically approved, most multi-agent DCE MRI studies are performed in animal models.

Diffusion Weighted Imaging MRI

With Diffusion Weighted Imaging (DWI), gradients placed prior to the signal readout are used to sensitize the MRI signal to the diffusivity of water molecules in the tissue. Due to kinetic energy, water molecules exhibit a continuous random motion. However, in tissue the intra and extracellular structures hamper this free diffusivity of water. By acquiring images with different diffusion weighting (b-values), quantitative information

about the diffusivity of water can be acquired. By fitting a mono-exponential function to the signal decay as function of diffusion-weighting, the Apparent Diffusion Coefficient (ADC) of the tissue can be determined. The ADC is a measure of how freely the water can move in the tissue, with higher ADC representing more freely moving water molecules. DWI has been widely applied in cancer imaging to determine tissue properties, treatment induced tissue changes and as prognostic marker. In PDAC, DWI has been used to describe and detect lesions [64, 65] and has been associated with tumor cellularity and patient outcome [66]. In esophageal cancer DWI is gaining more and more interest in detecting lesions and predicting and evaluating response to therapy [67].

Besides random motion, bulk movement of water molecules is present in the tissue microcirculation. This movement of water molecules in the microcirculation is generally faster than that of the random motion in the surrounding tissue. By adding images acquired at very low b-values, (0-200 mm/s^2) a second exponent can be added to the diffusion model, describing the faster movement of water molecules in small blood vessels. The most used bi-exponential diffusion model is the intra-voxel incoherent motion (IVIM) model, which has shown value in characterizing PDAC lesions [68–72] and esophageal cancer [73]. Although the IVIM model is the most used model to describe multiple b-value DWI data, there are many models that can be used to fit the data. For most of these models a basis can be found in physiological properties of the tissue [74]. However, not all models have a clear underlying physiological basis, which is especially important in understanding tumor biology, where standard hypothesis about biological function do not hold anymore [75].

T2 MRI*

T2* or R2* (=1/T2*) imaging can be used to generate an image contrast based on the magnetic properties of hemoglobin present in the blood vessels of the tissue. The paramagnetic properties of deoxy-hemoglobin [76] distorts the local magnetic field, resulting in a decrease in T2* relaxation time compared to areas containing more oxygenated, diamagnetic, hemoglobin. This technique is also referred to as blood oxygen level dependent (BOLD) imaging and is most often used in functional brain imaging. However, since hypoxic areas are prone to have more deoxygenated blood, the T2* of hypoxic areas can also be expected to be lowered compared to the surrounding well oxygenated tissue. Several studies have shown the relation, or the lack of it, between tissue oxygenation and T2* MRI in cancers [77–79].

Positron Emission Tomography

Positron emission tomography (PET) is an imaging modality where images are generated based on positron emitting radionuclides. The radionuclides are coupled to molecules with a specific biological or therapeutic function that act as carrier. The so formed tracers are injected into the body and accumulate at specific targets in the body based on the tracer properties. Meanwhile the radionuclide is emitting positrons, which when annihilating with an electron emit two photons in opposite direction. These photons can be detected by a ring of detectors surrounding the patients. Making use of the fact that the photons travel and are detected at opposite directions, the localization of the positron-electron annihilation can be reconstructed. This way an image can be reconstructed that shows the amount of tracer accumulating at a specific location in the body as contrast. These images are combined with CT, and more recently MRI, scans for anatomical information and attenuation correction. The most used PET-tracer in the clinic is fluor-18 labelled fluorodeoxyglucose or ^{18}F-FDG. With FDG PET glucose metabolism can be visualized, which is often elevated in highly proliferating tumors and therefore highly applicable in tumor detection and staging [80].

Hypoxia PET

Besides metabolism, PET tracers can be developed to target other cellular processes, such as cellular hypoxia. [21] The majority of hypoxia PET tracers are based on 2-nitroimidazoles. 2-Nitroimidazoles are able to freely diffuse across the cell membrane, where an oxygen-reduction reaction takes place immediately after entering the cell. The now formed reactive radicals can be re-oxidized in the presence of oxygen, enabling them to leave the cell again. However, in the absence of oxygen, the formed radicals are further reduced and react with macromolecules, trapping them within the cell [81]. This way the radioactive labelled material gets trapped in the hypoxic cells. In order to generate a contrast to the surrounding tissue the un-trapped activity must be cleared from the body, which takes place via the blood and kidneys. Examples of nitroimidazole based PET tracers are ^{18}F-FAZA, ^{18}F-MISO, ^{18}F-FETNIM, and ^{18}F-HX4, which have shown promising results in detecting hypoxia in both pancreatic and esophageal cancer [50, 82–84].

Advanced post-processing

Contrast enhanced CT imaging is the current standard for initial staging and follow-up of both pancreatic and esophageal cancer. Although this technique is valuable to determine tumor location and possible distant metastases, CT data is not typically used to determine tumor heterogeneity or disease prognosis. Advanced post-processing methods allow to extract quantitative imaging biomarkers from standard medical

images, as CT, MRI and PET [85]. By applying these methods, lesion features are extracted describing its intensity, shape and texture. Furthermore, a combination of advanced image filtering methods can be applied to these image intensity and structure parameters to further stratify heterogeneity. This way, several thousands of features can be extracted from a single tumor. By combining these features, prognostic phenotypes of individual lesions can be determined, which is often referred to as radiomics [86].

Aim & Outline

The general aim of this thesis is to characterize the tumor microenvironment of pancreatic and esophagogastric cancer by quantitative imaging and to investigate if these methods enable to monitor treatment and predict patient outcome in these cancers. We develop, validate and apply multiple imaging techniques and processing methods on multiple imaging modalities in both a clinical and pre-clinical setting to investigate the potential of imaging biomarkers in the clinical work-up of pancreatic and esophagogastric cancer.

Ideally treatment strategy is not only determined beforehand, but also adapted during its course. Early treatment evaluation could help to reduce continuing of unnecessary treatments, reducing both patient burden and costs. An important factor for faithful interpretation of longitudinal imaging data is the underlying repeatability of the technique. Changes in parameter values induced by treatment should at least be able to exceed the day-to-day changes measured when no treatment is given in order to be of any value. For most quantitative imaging techniques this information is unknown. Furthermore, besides physiological variations repeatability can be influenced by acquisition technique and hardware and post-processing methods. To get a full understanding of a methods repeatability, the entire pipeline should therefore be evaluated for each specific application. In **Chapter 2** the feasibility and repeatability to image tumor hypoxia using HX4 PET is investigated in both patients with esophageal and pancreatic cancer. **Chapter 3** describes the repeatability of both DCE and T2* imaging in PDAC patients and how the parameters from these two MRI methods are correlated. Next, IVIM MRI is further explored by using different methods to fit the IVIM model to DWI data and how this effects the repeatability of the resulting parameters in **Chapter 4**.

For both pancreatic and esophageal cancer it is know that neo-adjuvant response rates vary greatly and that some patients are even cured by it alone. Identifying response to neo-adjuvant therapy in an early stage of treatment would enable early adaptation of treatment. Quantitative imaging could be utilized to extract parameters that can help to facilitate this. In **Chapter 5** we aim to evaluate different models

to describe DWI data of pancreatic cancer to extract the most relevant parameters to detect the effects of treatment in patients with pancreatic cancer receiving neo-adjuvant chemoradiotherapy.

In order to enable a successful translation of these imaging methods into clinical practice, understanding of the biological processes reflected by quantitative imaging parameters is vital. Especially in cancers, where biology is disrupted, hypothesis about how imaging parameters reflect tumor biology are difficult to test. One way to achieve this is to directly compare imaging parameters to immunohistochemistry derived tissue properties from the same tissue sample. In **Chapter 6** and **Chapter 7** we utilize DCE, IVIM, T2* MRI and HX4 PET to investigate whether these techniques can be used to non-invasively characterize three important hallmarks in the development of pancreatic cancer; desmoplastic transition in the form of collagen deposition, (hypo) vascularization and the subsequent development of cellular hypoxia. Furthermore, we investigate if these quantitative imaging parameters can be used as biomarkers to predict patient outcome.

Esophageal cancer metastasis often manifests in one of the largest abdominal organs, the liver. In this phase of the disease, oncological treatment shifts from curative intent to palliative, intending to extend life or improve its quality instead of curing the patient. The effects of palliative treatment however vary greatly between patients. In **Chapter 8** we investigate the feasibility to use a CT based radiomics approach to predict response of individual liver metastasis to an often used chemotherapy in patients with advanced esophagogastric cancer. In **Chapter 9** we investigate the effects of anti-angiogenetic treatment in an esophageal cancer liver metastasis mouse model using a multi-contrast DCE MRI approach. Using these methods we intend to better understand the effects of the treatment enabling better timing of the treatment for an optimal effect.

In **Chapter 10** a general discussion and future outlook on quantitative imaging in the oncological practice of pancreatic and esophagogastric cancer are given.

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