Chapter 1

General introduction and Outline of the thesis

GENERAL INTRODUCTION

Metastatic disease to the liver is a very common clinical situation in oncology. The liver is one of the most common sites of metastatic spread of epithelial cancers, second only to regional lymph nodes. The true prevalence of metastatic disease is unknown, but approximately 20%-25% of patients with colorectal cancer have liver metastases at the time of diagnosis. Studies based on autopsy results showed that up to 70% of colon cancer patients have liver metastases at autopsy [1]. Further, Morana et al. [2] have shown in cadaver studies of primary colorectal carcinoma that on average at least one liver metastasis less than 10mm in diameter is missed for each detected liver metastasis larger than 10mm.

The early detection of liver metastases is of utmost importance in patients with cancer. In general, the presence of (relatively extended) liver metastases indicates non-resectability of the primary tumour for oncologic reasons [3], except for tumour palliation (i.e. to relieve obstruction of the gastrointestinal tract). In these patients, chemotherapy is the method of choice. Chemotherapy can also be used to decrease tumour load to allow subsequent surgical treatment. In many cases, chemotherapy is also used after surgery or ablation therapy as neo-adjuvant therapy. Resection of liver metastases of some malignancies (including colorectal cancer) has been shown to improve the survival of the patients [4]. The presence of limited synchronous colorectal liver metastases (i.e. occurring at the time of diagnosis of the primary tumour) or metachronous colorectal metastases (occurring after diagnosis of the primary tumour) warrants surgical resection [3].

Exact knowledge of the number, size, and regional distribution of liver metastases is essential to determine their resectability. In patients with liver metastases from colorectal cancer, hepatic resection has proven survival benefits and is curative in a small proportion of cases. Patients whose metastases are small, few in number and metachronous have the best prognosis, but there is now good evidence that patients with more extensive disease can benefit from resection [5-8]. The number, size and distribution of lesions are no longer limiting factors, provided all lesions are removed with adequate tumour-free margins and there is sufficient normal liver to maintain liver function postoperatively. Based on the number and localization of the liver metastases and considering all other clinical parameters of the patient, only about 30% of colorectal patients with liver metastases may undergo resection. However, the 5-year survival of these patients is between 30% and 48% in comparison to a survival of less than 5% of patients with liver metastases not amenable to liver surgery [4, 9-11].

IMAGING:

It is the task of imaging to evaluate the liver to assess the presence or absence of liver metastases in surgical candidates and to evaluate the success of chemotherapy or ablation therapy in others. Incomplete resection of colorectal liver metastases does not prolong survival [1], so knowledge of the exact extent of intra-hepatic disease is crucially important in determining patient management and outcome. Almost all liver metastases larger than 10mm are demonstrated with current imaging techniques but the detection of smaller liver metastases is still relatively poor [12-16].

US, CT, PET(/CT):

Transabdominal UltraSonography (US) is widely used to assess the liver, but has some limitations: it needs considerable operator expertise and often reveals equivocal results in patients with (chemotherapy-induced) fatty infiltration of the liver [17]. Contrast-Enhanced (CE)-US has increased potential in characterizing malignant and benign focal liver lesions compared with baseline US. CE-US increased diagnostic confidence in the detection and characterization of liver metastases compared with standard US [18]. Real-time CE-US is particularly advantageous in detecting small liver metastases, even when compared to CE-Multi-Slice Computed Tomography (MSCT) and Magnetic Resonance Imaging (MRI) [18-21]. CE-US with sulphur hexafluoride (Sonovue®) is comparable with CE-MSCT in the characterization of focal liver lesions [22, 23]. Limitations of CE-US are essentially the same as those of US and are related to the presence of bowel gas and to the patient's body habitus [24]. Among radiologic imaging techniques, US and CE-US is a relatively cheap technique and therefore is used in many general radiology departments [25, 26]. However, for accurate oncological staging, US examinations often are complemented by other imaging techniques.

Diagnostic problem cases using US are then often referred for a CT or MRI examination. With the introduction of MSCT imaging, the use of MSCT in oncologic patients to search for lung, liver, and lymph node metastases in the body has substantially increased [27, 28]. The development of MSCT has substantially increased patient throughput allowing volume coverage of the whole thorax and abdomen in one breath-hold. However, even using MSCT, the sensitivity and discrimination between small liver metastases and liver cysts is inferior

compared to MRI [27]. MRI with a liver specific contrast agent is therefore recommended for the preoperative evaluation before liver surgery for detection and characterization of liver metastases [27]. For the evaluation of lung metastases, imaging can be limited to chest radiography. In doubtful cases or potential candidates for surgery, CT of the chest can be performed [29].

Fluoro-18-DeoxyGlucose Positron Emission Tomography (FDG-PET) has been reported to be superior to CT for the detection of liver metastases from colorectal cancer [30-33] and was found to be the most sensitive non-invasive imaging modality for the detection of liver metastases [33, 34]. FDG-PET has also been described as the most accurate imaging technique to detect extrahepatic disease [29, 33, 35]. Direct comparison between MRI and FDG-PET has been limited, but would be critical for optimization of imaging at diagnosis and during follow-up.

Combined PET/CT images have significant advantages over either technique alone because it provides both functional and anatomical data. The most significant additional information provided by PET/CT relates to the accurate detection of distant metastases. PET/CT should be performed on selected patients with possible but inconclusive metastatic lesions with CT [36]. The incremental value of integrated FDG-PET/CT imaging compared with either technique alone in a study by Roman et al. resulted in incremental diagnostic value of integrated PET/CT imaging in 27% and incremental impact on management in 12.5% of patients [37]. In a study by Wiering et al. FDG-PET was clearly superior to CT in predicting extrahepatic disease in patients with colorectal liver metastases [35].

Magnetic Resonance Imaging:

MRI is still limited in anatomic coverage, although the recent introduction of multi-channel MRI coils with wider coverage and the moving-table MRI technique has re-established the competitiveness of MRI with MSCT with regard to patient throughput. One of the advantages of MRI in liver imaging is the better soft tissue contrast, which reveals better characterization of focal liver lesions in question. The development of liver-specific MRI contrast agents has further improved the diagnostic yield of MRI in lesion detection and characterization [38]. Although the primary modalities for liver imaging are US and CT, recent studies have suggested that CE-MRI is the most sensitive method for detecting small liver metastases and MRI is now considered the preoperative standard [39-43]. Developments in MRI hardware and software and the availability of novel MRI contrast agents have improved small focal liver lesion detection [1]. During the last years, MRI enhanced with SuperParamagnetic IronOxide (SPIO) probably has been considered the most sensitive method for detecting liver metastases [1]. In the few studies which have compared the different liver specific agents, SPIO-enhanced MRI has demonstrated varying degrees of superiority, particularly for small focal liver lesions [44, 45]. Furthermore, the importance using ferucarbotran (SPIO contrast agent) by bolus injection and providing the opportunity to obtain dynamic T1w images has been described [1]. Ward et al. [1] has found early T1 enhancement on 3D fat-suppressed T1w Gradient Echo images to be particularly valuable for depicting small focal liver lesions. The T1 effect is considerably less than occurs with extracellular fluid gadolinium-based contrast agents but this is often beneficial in the context of metastatic disease. Liver and vessels

often have a similar signal intensity which produces a virtual blank canvas against which small liver metastases are extremely conspicuous and reliably distinguished from vessels. The combination of thin-slice 3D T1w and T2w imaging after SPIO increases diagnostic confidence and is more accurate for small focal liver lesion detection than delayed T2w imaging alone [1].

Mangafodipir trisodium (Mn-DPDP, Teslascan®, Nycomed, Oslo, Norway) significantly enhances the liver parenchyma in the delayed phase. Tumours of non-hepatocellular origin show little or no contrast-enhancement resulting in increased lesion conspicuity in the delayed phase. Uptake of Mn-DPDP by both benign and malignant hepatocellular tumours limits the accurate differentiation between benign and malignant focal liver lesions. The ensuing lack of a dynamic imaging capability is a disadvantage and has led some authors to propose the possibility of sequential administration of Gadolinium chelates and Mn-DPDP in a single visit to obtain both dynamic and delayed imaging [38].

Diffusion-weighted imaging (DWI):

Diffusion-weighted MRI is sensitive to molecular diffusion due to random and microscopic translational motion of molecules, known as Brownian motion. Random motion in the field gradient produces incoherent phase shifts that results in signal attenuation. Flowing spins induce the same attenuation effect; the pseudorandom organization of the moving spins at the voxel level, such as perfusion, can also be considered to be an incoherent motion, and this effect can induce much larger signal attenuation than the diffusion effect on an image with very low Motion-Probing Gradients

(MPGs) [46, 47]. The strength of the applied MPG increases with increasing b-value (expressed in s/mm^2). On the basis of this theory, the Apparent Diffusion Coefficient (ADC) value calculated from the images with no and low MPGs (ADC_{low}) is considered to be more strongly influenced by the flowing spins (microcirculation) than molecular diffusion. The true diffusion coefficient (D) can be obtained from the calculation from images with the higher MPGs [46, 47]. D as measured at IntraVoxel Incoherent Motion MRI is a true parameter of molecular diffusion [46, 47]. It therefore permits characterization of tissues and pathologic conditions. Furthermore, the perfusion fraction f as measured at IntraVoxel Incoherent Motion MR imaging is the (microperfusion) deviation factor representing the fractional volume (of spins) occupied in the voxel by flowing spins (= sum of the spins in the microcirculation and spins in turbulent flow).

Diffusion-Weighted Imaging (DWI) using Echo Planar Imaging (EPI) in the liver is useful for the detection of focal liver lesions because of the black-blood effect when using low b-values. The black-blood effect renders blood vessels black while focal liver lesions remain bright. The use of the black-blood effect for facilitating detection of focal liver lesions - by better differentiation between small vascular branches and small focal liver lesions - has been described previously [48]. This black-blood effect might be useful in detecting focal liver lesions.

Single-Shot Spin Echo Echo Planar Imaging (SS SE-EPI) in this thesis is used with different b-values. The lower b-values are mostly useful for focal liver lesion detection and the higher b-values for focal liver lesion characterization. The SS SE-EPI sequence is prone to susceptibility artifacts (e.g. air from the bowel loops). Therefore, each patient is given some water just before the start of each MRI examination. In this thesis, the SS SE-EPI sequence is

performed as the first sequence during each MRI examination during respiratory triggering.

Perfusion MRI:

After the detection of focal liver lesions, the differentiation of benign from malignant focal liver lesions is a next crucial step. The rim surrounding malignant focal liver lesions on MRI has been evaluated in the past as a useful sign for distinguishing malignant from benign tumours [2]. To date, reports of liver perfusion at MRI have been limited and vary considerably [49]. T1w dynamic CE-MRI seems a promising method for the detection of cancer [50]. Remarkably, encouraging results have been obtained despite considerable variation in both the methods of data acquisition and analysis (e.g., visual inspection [51], parametric analysis [52], pharmacokinetic [53] or physiologic [54] modeling). In most cases, only one to a few slices within the whole liver parenchyma have been used to evaluate perfusion parameters.

Thanks to new developments in MRI scanning technologies, it is now possible to perform T1w CE-MRI of the entire liver with high spatial and temporal resolution (using a so-called 4D THRIVE sequence). In this thesis, the 4D THRIVE sequence is evaluated for its ability to differentiate benign from malignant focal liver lesions.

OUTLINE OF THE THESIS

In this thesis, new developments in diffusion weighted MRI (SS SE-EPI DWI) and perfusion MRI for liver lesion detection and characterisation are presented which were studied in different cohorts of patients suspected of colorectal liver metastases. The studies were performed in a tertiary referral center.

In **chapter 2** a respiratory-triggered fat-suppressed T2-weighted Turbo Spin Echo (RT FS T2w TSE) and breath-hold fat-suppressed T2-weighted Turbo Spin Echo (BH FS T2w TSE) sequence were prospectively compared for the evaluation of focal liver lesions. Qualitatively analysis was performed for image quality, lesion conspicuity, diagnostic confidence, artifacts and quantitative analysis was performed for lesion-to-liver CNR. The detection and characterization of focal liver lesions in patients suspected for colorectal liver metastases was evaluated.

In **chapter 3** the potential of SS SE-EPI DWI for the detection of focal liver lesions (biliary cysts, hemangiomas and metastases) with different sizes (<10mm, 10-20mm, and >20mm) was prospectively compared with T2w SS TSE. A qualitative and quantitative comparison of a respiratory-triggered SS SE-EPI DWI sequence with four b-values (b=0, b=20, b=300, b=800s/mm^2) and T2w SS TSE was made. The detection of focal liver lesions in patients suspected for malignant liver lesions was evaluated with special focus on small (<10mm) focal liver lesions.

In **chapter 4** the primary purpose of this prospective study concerned the differentiation of liver metastases and liver hemangiomas by quantitative evaluation of D, f and ADC_{low} using a respiratory-triggered BB SS SE-EPI sequence with four b-values (b=0, b=10, b=150, b=400s/mm^2). The potential of BB SS SE-EPI as a useful technique to aid in differentiating between liver

metastases and liver hemangiomas by calculation of D, f and ADC_{low} and its potential in avoiding liver biopsies was evaluated.

In **chapter 5** SS SE-EPI using b=0, 10, 150, 400 s/mm^2 was prospectively compared with standard MRI techniques after intravenous SPIO. Best lesion detection respectively best image quality was compared between SS SE-EPI and standard SPIO-enhanced MRI sequences. Lesion characterization was compared between SS SE-EPI and standard MRI sequences pre- and post-SPIO. The detection and characterization of focal liver lesions in patients suspected for metachronous liver metastases from colorectal carcinoma was evaluated with special focus on small (<10mm) focal liver lesions.

In **chapter 6** the accuracy of FDG-PET/CT and MRI (including SS SE-EPI and SPIO-enhanced MRI) were prospectively compared for the detection of liver metastases from colorectal cancer. The sensitivity and positive predictive value for the detection of colorectal liver metastases was studied. The potential of both MRI and FDG-PET/CT was evaluated for the detection of colorectal liver metastases.

In **chapter 7** a prospective comparison between SS SE-EPI DWI before, immediately after and 5 minutes after intravenous injection of SPIO, between non-CE and post-SPIO T2w TSE sequences was performed for the detection and characterization of focal liver lesions. A comparison between SS SE-EPI DWI before, immediately after and 5 minutes after intravenous injection of SPIO evaluating image quality was performed. The potential of SS SE-EPI and the effect using SPIO with different time delays on image quality, detection and characterization of focal liver lesions was evaluated.

In **chapter 8** a newly developed perfusion imaging sequence (4D THRIVE) was prospectively evaluated using 3T MRI. Imaging of the whole liver in high temporal and spatial resolution was performed. The potential of 4D THRIVE for perfusion imaging of the whole liver and automatically calculated parametric maps was prospectively evaluated for the characterization of focal liver lesions.

In **chapter 9** the feasibility to incorporate phospholipids, derivatized with a metal complexing moiety, into a magnetoliposome (ML) coat and to load the resulting nanocolloids with gadolinium ions was evaluated. The main goal of this paper was to study the feasibility to construct a corona of lanthanide ions on top of nano-sized MLs.

In **chapter 10** the feasibility to correlate peri-tumoural vasculature (ring-enhancement) surrounding colorectal liver metastases after intravenous injection of magnetoliposomes using T1-weighted MRI in a rat model was evaluated. A proof-of-principle was given correlating peritumoural ring-enhancement on T1-weighted MRI after intravenous injection of magnetoliposomes with histopathology.

Finally, the results of this thesis are summarized and implications are made.

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