General introduction and aims of the thesis

GENERAL INTRODUCTION AND AIMS OF THE THESIS

The incidence of focal liver lesion is increasing. It is probably due to widespread availability of modern radiological imaging. Ultrasound, CT or MRI can detect some liver lesion in up to 1/3 of examinations in general population [1]. The majority of these incidentally detected lesions are benign, but malignancy should be always ruled out. As management and prognosis varies greatly, correct diagnosis is important. The most common benign liver lesions are simple cysts, focal steatosis, haemangiomas, focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA). Some are completely innocent and their correct and proper diagnosis is the most important step in clinical work-up. Others can have a different course over time. They can be complicated by bleeding or rupture. Some have even potential to undergo malignant transformation over period of years. Thus, in clinical practice, discrimination inside benign tumors group is important, but discrimination between benign and malignant is of utmost importance.

Focal nodular hyperplasia

FNH is a tumor-like malformation consisting of hyperplastic nodules of hepatocytes, separated by fibrous septa, which form a typical central scar [2]. The liver is otherwise morphologically and histologically normal. FNH can be defined as not truly a tumor but a local regenerative mass of normal polyclonal hepatocytes. The prominent central artery lies close to the central scar. The lesion is often found incidentally during an imaging session for unrelated complaints. It may be detected more frequently in women and in 15% to 30% of cases, FNH is multiple [3]. FNH is a benign lesion with no malignant transformation course, the chance of bleeding is very low. If properly diagnosed, specific treatment is very rarely indicated.

Hepatocellular adenoma

Hepatocellular adenoma is a benign neoplasm that originates in a normal liver and is composed of cells that closely resemble normal hepatocytes [2]. Adenomas typically develop in women during the reproductive age, and are almost always associated with oral contraceptive use [4]. They have been also reported in patients with an inherited glycogen storage disease and maturity-onset diabetes of the young, and some are obesity-related. Approximately 33%–80% of patients are asymptomatic with tumors discovered by a chance on imaging [4-5].

Recently a new molecular classification has been established, based on metabolic pathways [6-7]. There are currently four suggested subtypes of liver adenomas: 1) Hepatocyte nuclear factor 1 (HNF1-α)-inactivated adenomas (25%–40%, diffuse intratumoral steatosis), 2) β-catenin mutated (5%–10%), 3) teleangiectatic/inflammatory

(45%–55%, former teleangiectatic focal nodular hyperplasia [FNH]), and 4) unclassified (5%–10%). MRI is the best imaging modality for characterizing HCA, and efforts based on MRI imaging are being made to subclassify them in accordance with the above-mentioned metabolic subtypes [8].

Adenoma may require more invasive treatment. This profoundly differs in relation to FNH and in some cases, a correct differential diagnosis can be challenging against FNH. Adenomas can be complicated by spontaneous rupture, bleeding and even malignant transformation (into hepatocellular carcinoma). Therefore HCA diagnosis is highly important. The most important factor for treatment is size of the tumor. Complications very rarely occurs in HCA smaller than 5 cm. The first step in the treatment of HCA consists of weight reduction (in obese patients) and cessation of oral contraception, with reevaluation after 6 months. Surgical treatment is recommended in all patients with β-catenin mutated variety and all males.

Benign versus malignant focal liver lesions

Contrast-enhanced ultrasound is highly capable of differentiating between benign and malignant liver lesions. The level of accuracy is the same for lesions that are < 2 cm and those that are > 2 cm. CE-US shows sensitivity and specificity above 85%, positive and negative predictive values (PPV and NPV) of 92% and 77%, respectively, and accuracy of 86% [9-10]. The detection of hypoenhancement (wash-out) during the portal or late phase is strongly suggestive of a malignancy in which >90% of malignant lesions show this feature [11-12]. The presence or absence of preexisting diffuse chronic liver disease is an important factor in interpreting CE-US results. In patients with liver cirrhosis, all solid lesions should be regarded as potentially malignant, unless proven otherwise.

A comprehensive review from the National Institute for Health research of the UK strongly stated: “A potential advantage of using CEUS would be the option of completing the assessment at the same time as the initial unenhanced ultrasound…. to provide more rapid diagnosis without repeat hospital visits is likely to be preferred by patients and may also reduce costs.“ [13]

Aims of this thesis

The overall aim of this thesis was to address various aspects of diagnostic contrast-enhanced US and its diagnostic capabilities in relation to benign and metastatic liver tumors, to other radiological methods, its cost-effectivity and various topics related to its use.

The basic questions related to CE-US diagnostics are: “Is the lesion in the liver benign or malignant?” and “What kind of benign (malignant) lesion is it?” [14]. Position of liver CE-US in imaging algorithms is not precisely stated yet. It is positioned

somewhere between quick, generally available, cheap but unspecific and less sensitive B-mode ultrasound and highly specific, costly and academic contrast- enhanced MRI. Questions arise. What is the position of CE-US in relation to other radiological methods (MRI, CT)? Where does it stand in solid benign liver lesions diagnostics and where in ruling out malignancies? Can we make proper diagnosis immediately during first examination or should we use some more specific method later? What CE-US features should we look for and what is their value in relation to others? Can we improve CE-US results by adding another modern imaging technology, such as stiffness measurements? Is CE-US in focal liver lesions diagnostics cost-effective? Currently there is no widespread consensus regarding the optimal management of CEUS and its position in focal liver lesion diagnostics.

In **chapter 2** (*The state of contrast-enhanced ultrasound imaging in benign focal liver lesions: Where are we now?*) we outline current concepts and status of CE-US and its development. The aim of this chapter is to demonstrate the characteristic features, and CE-US diagnostic position in focal liver lesion diagnostics. This chapter is also a brief review of the literature related to the topic. CE-US can substantially help in a differential diagnostic workup.

Continuing along this theme, in **chapter 3** (*Performance of contrast-enhanced sonography versus MRI with liver-specific contrast agent for diagnosis of hepatocellular adenoma and focal nodular hyperplasia*), we evaluate the position of CE-US in relation to the golden diagnostic standard (MRI with liver-specific contrast agent) for diagnosis of the two most important benign liver lesions - focal nodular hyperplasia and hepatocellular adenoma – in a large cohort of patients.

Chapter 4 (*Can point shear wave elastography differentiate focal nodular hyperplasia from hepatocellular adenoma?*). Recently, a new technique for quantifying local stiffness has emerged. Shear wave elastography technology can provide additional information from tumors, and FNH is a natural candidate for exploration. In some reports, it has been shown that FNH has higher stiffness compared to other focal liver lesions [15]. Whether focal elastography can be a complementary tool to CEUS or not still waits further validation [16].

This chapter focuses on the question as to whether point shear wave elastography can differentiate focal nodular hyperplasia from hepatocellular adenoma. When the diagnosis remains uncertain, these patients may undergo a tumor biopsy. In order to avoid a percutaneous biopsy and the associated risk of complications or even the surgical resection of a suspect lesion that turns out to be FNH, improvement of the diagnostic process is needed.

In **Chapter 5 (***A model-based prediction of the probability of hepatocellular adenoma and focal nodular hyperplasia based on characteristics on contrast-enhanced ultrasound*), we describe the development of a model-based prediction for the probability of hepato-

cellular adenoma and focal nodular hyperplasia based on CE-US characteristics. The main objective was to determine how frequently the specific features of HCA and FNH are displayed on CEUS. We also sought to define the predictive value of features for the discrimination between HCA and FNH on CEUS, and a specific formula for adenoma prediction is the result

Chapter 6 (*Liver contrast-enhanced ultrasound improves detection of liver metastases in patients with pancreatic cancer*) goes on to malignant liver metastases of pancreas adenocarcinoma as such lesions type is important in differential diagnosis of liver focal lesions. Thus far no study has evaluated the performance of CE-US compared to CT scan, in assessing liver metastases of patients with suspected pancreatic adenocarcinoma, this study is the first one ever performed. Should we use CE-US in a pre-operative work-up in patients with a known extrahepatic malignant tumor?

In **chapter 7** (*Clinical and economic evaluation*) we evaluates economic aspects of CE-US examination in a patient with an already diagnosed focal liver abnormalities. The main advantage of our study consists of adding a treatment phase to diagnostic one, and we ask whether CE-US has a role in cost-effectiveness?

Chapter *8 (Inflammatory and multiple hepatocellular adenoma are associated with higher BMI)* describes different subtypes of hepatocellular adenomas in relation to other clinical aspect, such as higher body mass index (BMI) and multiple and inflammatory varieties. We investigated whether the presentation of single or multiple adenomas may lead to different management strategies.

Finally, in **chapters 9 and 10** we summarize results and continue to a conclusion for this thesis.

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