Imaging of hepatic hypervascular tumors & clinical implications
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CHAPTER 1

Imaging of Hepatic Hypervascular Tumors & Clinical Implications

Introduction
Different tumors can arise in the liver. Some of these tumors are found by accident on imaging performed for an unrelated cause and some tumors manifest with symptoms. To determine the nature of the tumor imaging is performed to narrow down the differential diagnosis. If diagnosis remains inconclusive a biopsy of the tumor can be performed to evaluate the tumor with immunohistochemical analysis. The first step in diagnosis is to determine if the lesion is benign or malignant. And patients with a malignancy will be taken through the diagnostic work-up urgently to determine the stage of disease and initiate appropriate treatment. When patients with a benign tumor do not present with life-threatening complications, time is not essential for survival and the differentiation between benign hepatic tumors can be performed at a slower pace.

**Benign liver tumors**

The most common benign hepatic tumor is the hemangioma, occurring in the general population with incidences ranging from 0.4 to 20% [1]. Hemangiomas are composed of multiple, large vessels. Most hemangiomas are discovered at the mean age of 50 years and are seen more often in females [2]. The etiology is not understood, although a congenital anomaly has been suspected [1, 3]. Most hemangiomas are small, asymptomatic and are usually incidental findings. Since the lesion is benign, these hemangiomas usually require no treatment or follow-up. Hemangiomas >5cm are designated giant hemangiomas and because of size, may give rise to symptoms. Differential diagnosis includes other hypervascular tumors, such as hepatocellular adenoma and hepatocellular carcinoma. The second most common benign liver tumor is focal nodular hyperplasia (FNH). Most people will not know they have an FNH as the lesion rarely causes complications, symptoms or discomfort. FNH is predominantly found in women in their child bearing years. The etiology of this tumor is unknown, but is thought to be a hyperplastic response to (vascular) damage in the liver [4-6]. FNH is not associated with risks [4] and invasive treatment is not advised. Hepatocellular adenoma (HCA) on the other hand does hold risks of complications and is closely associated with hormone levels. HCA is predominantly seen in young women and prolonged use of oral contraceptives has been documented to influence growth of HCA [7]. This benign hepatic lesion might undergo malignant transformation in a small percentage of lesions [8]. Clinically more relevant is spontaneous rupture and bleeding of the tumor, causing pain and in some cases life-threatening hemorrhage [9]. Therefore, patients at risk for these two complications are advised to undergo preventive resection of the tumor(s). Diagnosis and treatment of benign hepatic tumors is not always straightforward and can cause confusion for both patient and treating physician.
physician. In this thesis we mainly focussed on differentiating HCA from FNH using different imaging modalities along with treatment advises.

Hepatocellular Carcinoma

In the past decade the incidence of hepatocellular carcinoma (HCC) in the Western world has increased. In the Netherlands we have seen an increase from 340 new patients with primary liver cancer in 2001 to 544 in 2011. Since 2008 a multidisciplinary team has been assigned in our institution to deal with diagnosis and treatment of this patient group. HCC usually develops in the background of cirrhosis and parenchymal disease including hepatitis. Patients with known risk factors for HCC are screened every year with ultrasonography of the liver. When a suspicious tumor is found additional imaging is performed to confirm diagnosis of HCC. Various treatment algorithms have been proposed and the latest update of the guideline used at the AMC was by the European Association for the Study of the Liver (EASL) in 2012. The best outcome for survival is early stage of the disease with minimal tumor load, thereby increasing chances of curative treatment. However, most patients (approximately 70%) have intermediate to late stage of the disease and are treated with palliative or symptomatic care. In this thesis, detection and diagnosis of patients with HCC are dealt with to improve staging of HCC lesions ultimately resulting in more accurate treatment choices.

References

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The aim of this thesis was to evaluate diagnostic strategies and their clinical implications in patients with hypervascular hepatic tumors. The images of these tumors are shown with MR, CT and $^{18}$F-FCH PET/CT imaging.

Chapter 1 is the introduction of the thesis. Chapter 2 describes hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH); two benign hepatic tumors primarily seen in women between 20 – 60 years of age. We asked ourselves if MR imaging with Primovist® is of additional value for differentiation between both lesions. Another modality that we evaluated to differentiate HCA and FNH was the PET/CT with $^{18}$fluorocholine ($^{18}$F-FCH) tracer Chapter 3. No complications are known of FNH and therefore there is no indication for invasive treatment. HCA on the other hand is known to give complications: a rare chance of malignant transformation and clinically more relevant, the chance of spontaneous bleeding or rupture of the lesion. Surgical intervention for HCA is therefore indicated in patients who are at risk of these complications. In Chapter 4 we assessed the outcomes of surgical intervention in a cohort of patients with HCA or FNH. If the risk factors for bleeding in HCA were more clearly defined, the selection of patients to undergo (preventive) intervention would be more accurate. Therefore we first of all proposed a grading system with increasing severity for bleeding in Chapter 5. In Chapter 6 we set out to determine patient characteristics and lesion characteristics associated with the risks of bleeding in HCA.

In Chapter 7 the 6th most common malignancy worldwide is discussed: hepatocellular carcinoma (HCC). To improve detection of intrahepatic disease and extrahepatic extent of disease we hypothesized that the $^{18}$F-FCH PET/CT could be of additional value. While imaging modalities have become more and more of importance Chapter 8 evaluated if staging laparoscopy (SL) for patients with HCC is still useful. In Chapter 9 an overview is given of the HCC patient population and of management of the disease at the Academic Medical Center Amsterdam, The Netherlands.

Chapter 10 shows the images of four interesting cases pertaining to different hepatic tumors: hepatoblastoma, HCA with hepatic granulomas, giant hemangioma, and FNH with bile duct hamartomas. This thesis finishes with a discussion including future perspectives, a summary, and conclusions in Chapter 11.
A great deal of the intellectual effort of the last hundred years has been spent visualizing what was once invisible, visually penetrating the deepest recesses of mind and body. Naked to the Bone [1]

Our minds are constantly flooded by images from the world around us. We enjoy art, we love the movies, and take pictures of occasions we want to hold on to forever. In that respect, images are a way to communicate and can make us reflect on our view on the world, see another side of things, and show us what we cannot see with our own eyes. When it comes to medicine, we need images to help us in the diagnostic process, evaluate treatment options, and guide and follow-up the chosen path.

In 1895 Wilhelm Röntgen discovered ‘A new kind of light’ to write an image [2]. The mechanism depends on the capture of electromagnetic radiation (X-rays) on photographic plates. X-rays are absorbed in various degrees by tissues where the air in lungs hardly absorbs X-ray, and bone absorbs most of the radiation. The result is that lungs appear in black, tissues in various shades of gray, and bones in white on an X-ray image. Röntgen discovered the medical potential of X-ray when he portrayed the hand of his wife. Not just the healthy human body was displayed but also the broken and diseased. Shortly after its discovery the X-ray machines were introduced in the medical practice and were soon used throughout the medical world [3, 4]. That X-rays have a downside became clear by the burns and ulcers occurring on X-ray machine operator who were exposed for a longer period of time. The best documented case might be of Thomas Edison’s chief assistant Dally, dying an agonising slow death by the malignant consequences of the X-ray. Only 3-4 years after starting his work Dally had chronic ulcers on both hands, eventually leading to malignancies and he required amputation of his fingers, hands, and eventually arms until his death in 1904. Edison took a different path in his research and refused to undergo X-ray in the remainder of his life [1].

The history of whole body imaging has a more positive note with a combination of Röntgen’s technology, mathematics, and music. Electric and Musical Industries Ltd. (EMI) signed the young rock group ‘the Beatles’ in 1962 [6] 7, and due to their world-wide success the company had a great deal of money to invest. In the early days of EMI the Company was closely involved in research project and with the extra cash flow of the record industry they could invest even more. Godfrey Hounsfield [7] 8 was one of the researchers who profited. He proposed to combine Röntgen’s X-rays with Allan Cormack’s [5, 8, 9] 3,9,10 mathematical hypothesis and their collaboration enabled the build of the first computed tomography (CT) scanner. The computed tomography scanner

Never in the history of science has a great discovery received such prompt recognition and has been so quickly utilized in a practical way as the new photography which Professor Röntgen gave to the world only three weeks ago. Already it has been used successfully by European surgeons in locating bullets and other foreign substances in human hands, arms and legs and in diagnosing diseases of the bones in various parts of the body.

Historic interlude
or EMI scanner [9, 10, 101]. In October of 1971 the scanner enabled imaging of a patient’s brain with a cerebral cyst at Atkinson Morley Hospital in London [11, 12]. By 1975 the whole body instead of solely the brain could be observed in thin slices. The summary of the Nobel Prize awarded to Hounsfield and Cormack in 1979 says quite poetic that the CT scan ‘has ushered medicine into the space age’ [13].

Nobel Prize winner in Literature Harry Martinson tells how, one day, the mimarobe, the computer guardian, “...by means of Mima’s formula cycles, phase by phase ...saw into the transformations...” and was able to “...see through everything as though it were glass...” Nobel Prize 1979 [5]

Nuclear Magnetic Resonance

The downside of CT imaging is radiation exposure of X-rays. Therefore other possibilities were evaluated to image the human body without side effects. One of those proposed techniques was based on the atomic structure of water (protons) in the human body. When a liquid is placed in a high magnetic field these protons align with the direction of the magnetic field. A radio frequency current creates an electromagnetic field. As soon as the electromagnetic field is turned of the protons return or relax to their original equilibrium. During this process of relaxation electromagnetic radiation is generated and detected by receiver coils. Professor Raymond Damadian [14] worked on the basic principles of MR imaging for medical purposes and published his ideas in Science 1971 [14] and images of the first ‘live human body’ in 1977 [15]. Sir Peter Mansfield [physicist at the University of Nottingham], and professor Paul C. Lauterbur [16, 17] (physicist at the University of Illinois) were the other major scientists in the field. It turned out difficult to make the scanning fast enough to be practical and to translate the scan to visual images. In 1977 Sir Peter Mansfield succeeded to perform an MRI in seconds rather than hours and to translate the scan to actual images. In the 80’s MR imaging developed into a more sensitive modality as a higher field-strength became available: the 1.5 Tesla. Most imaging is still performed with this Tesla.

Positron Emission Tomography

First work was performed in very different sciences and was dosed with a good deal of luck. After Rontgen’s discovery of X-rays the entire scientific world was experimenting with the ‘new rays’ and there potential. Henri Becquerel [18] took uranium salt with the aim to evaluate X-rays had anything to do with naturally occurring phosphorescence (which had been the subject of his doctoral thesis). For this experiment he placed the salt rocks near a photographic plate and waited for the sun to eliminate the crystals. After a few cloudy days Becquerel discovered that even without direct sunlight the rocks had given of some radiation that left a dark imprint on the photographic plate (1896) [18]. His discovery intrigued Marie Curie who was in search of a subject for her doctoral thesis. She pursued the study of the uranium rays (or radiation) and was soon joined by her husband Pierre [19]. Daughter Irène Joliot-Curie and husband Frédéric Joliot-Curie continued in their academic footsteps and discovered artificial radioactivity in 1934 [20], the year Madame Curie died of leukemia due to the years of unprotected work with radiation. The world was overwhelmed by images of the inner body and new radiation. Science that wasn’t this mind-blowing was just not interesting. So with less uproar biologists discovered the ‘luminescence phenomena’ in the early 1900 [21]. Dr. Herly [22] described that ‘by means of ultraviolet light selective differentiation of tissues’ can be made, and Dr. Moore build on that idea to differentiate normal from malignant tissues by injected the dye sodium fluorescein [23]. In his later studies Moore would substitute the dye with radioactive isotopes including radioactive iodine and the first steps to nuclear medicine were made [24-26]. The development of radioisotopes that could be used in radioactive tracers to detect malignancies [27] was done by Merrill Bender (M.D.), and his research partner Monte Blau (PhD in chemistry) [28]. They developed an imaging technique to localize a brain tumor and soon studies with imaging agents like albumin [29], pancreas [30], and liver [31] and many other organs and organic systems followed. The first scanner was called the ‘head-shrinker’ and was built in 1961 by Dr. Robertson and colleagues at the Brookhaven National Laboratory. Dr. Fowler developed the fluoroxyglucose tracer which is still used today in positron emission tomography (PET) [32]. When PET was combined with CT imaging it was declared ‘the medical invention of the year’ by TIME magazine in 2000 [33]. MR imaging can also be used for topographic mapping of the PET image. Before undergoing the PET a short-lived radiopharmacon (tracer) is intravenously administered. The most commonly used tracer is an analogue of glucose: 18F-fluorodeoxyglucose (18FDG). The tracer will undergo decay: it emits a positron, which loses kinetic energy and interacts with an electron. This interaction results in a pair of gamma photons moving in opposite direction. These photon pairs are detected by the PET scanner and converted to a digital image. The scan shows a functional image of the human body and is combined with CT or MR imaging as topographic reference. When combining both imaging techniques a reconstruction of the body can be made and a specific localization of high metabolism of the used tracer can be detected.

In medicine we have gotten used to seeing beyond the exterior. An image tells a story and if we can relate to the picture we can’t help but get involved. Quite literally, images of the human body get under our skin.

Naked to the Bone [1]