Discussion and future perspectives

DISCUSSION AND FUTURE PERSPECTIVES

When a patient has diagnosed a focal liver lesion (FLL) for the first time, the main question is whether the lesion is benign or malignant. Due to widespread availability of modern radiological imaging, the incidence of detected liver tumors is increasing. Approximately 30% of general population has some type of focal lesion [1]. The majority of these incidentaly detected lesion are benign (cysts, hemangioma, adenoma, focal nodular hyperplasia), but malignancy (such as metastasis) should be always ruled out. Precise imaging diagnosis is of high importance, as their management and prognosis varies greatly. For liver imaging, the impact of the increased interest in liver diseases has been significant [2-4]. In general, unenhanced liver ultrasound (B-mode US) has not played a significant role in specific tumor diagnosis. Information concerning tissue perfusion was always missing. The advent of microbubble imaging has changed this concept. As contrast agents used in US (CE-US) move completely to the intravascular compartment, we can visualize perfusion in tissues, and information can be obtained in real-time. The role of contrast agents in US are somehow similar to the role they play in CT or MRI. Without intravenous contrast agents, these imaging modalities would also lack most of their diagnostic power. In a case of CE-US, we retain one of most important qualities of ultrasound that is its flexibility in everyday clinical practice. To date we have not defined specific role of CE-US in diagnostic work-up of liver tumors [5-6]. One may question how many patients with liver lesion suspected to be benign may by finally diagnosed by the means of CE-US only or how many and under which conditions they should be send to additional diagnostics (MRI, CT)? In this thesis, the author examined the position of CE-US and its role in management in the field of focal liver lesions (FLL).

CT or MRI is the most commonly imaging used for characterizing focal hepatic lesions [7]. However, the position of liver CEUS is now more settled. According to current WFSUMB guidelines – update 2020 [8] – is CEUS recommended in patients in the non-cirrhotic liver with inconclusive findings at CT or MRI imaging or inconclusive focal liver lesion biopsy. Contrast-enhanced CT and/or MRI are preferred modalities. Sometimes they are even contraindicated. Guidelines also stated, if CEUS has definitely characterized a benign FLL, further investigations are not necessary to confirm the diagnosis. Our study suggests a more restricted approach.

Liver adenoma (HCA) and focal nodular hyperplasia (FNH) are two most important benign lesions. FNH and HCA are two lesions that are sometimes mutually misdiagnosed, but their management and prognosis differs. It is of utmost importance to learn specific features and real-time dynamics of both of these lesions. At present, both CE-US and MRI are best regarded as complementary for diagnosing HCA and FNH [9]. In our large study, CE-US resulted in a conclusive diagnosis (HCA versus

FNH) in 92% of the cases, whereas MRI correctly diagnosed 99% of cases. In discordant cases, CE-MRI is highly accurate and superior to CE-US in histopathology-confirmed diagnoses [10]. We conclude that CE-US is less suitable as a stand-alone imaging modality for the final diagnosis of HCA of FNH. It has an adjunct role in discordant cases in patients in whom a quality MRI cannot be obtained, or reliably interpreted and in which liver biopsy is contraindicated. Perhaps in some less developed countries, where proper CT and MRI are not available.

What are these specific HCA and FNH features visualized by CE-US? In general, different benign tumours show different enhancement patterns. Benign liver lesions are mainly characterized by traits in the arterial phase. Portal or late phases are not so important. By comparison, some of patterns cannot be properly appreciated on CT or MRI scans because patterns change very rapidly. Using CE-US, we display microbubbles filling in real-time, and we use a frequency around 20 pictures per second (Hz) [11]. Our study in 324 patients with HCA or FNH described various more or less specific diagnostic features of the lesions [12]. Finally, we composed a calculus of predicted HCA probability using those various features. Approximately, 20% of FNH lesions lack typical CE-US morphological or perfusion features and thus can decrease proper diagnosis based on contrast agent perfusion characteristics.

Compared to men, women are more frequently diagnosed with these tumors, namely HCA and FNH. This phenomenon is probably related to higher estrogen levels [13]. In case of an HCA, the influence of oral contraception is also suspected as well [14-15]. Another putative reason for the rising HCA incidence is the increase in overweight/obesity in the population [16]. Significantly higher BMI is related to multiple adenomas [17]. Our findings, as well as reports from other authors indicate that in an obese patient, US is often difficult to perform. CE-US can provide some additional information about the nature and number of lesions and influence the decision as to surgical or non-surgical treatment. In a patient in whom physicians are reluctant to perform a lesion biopsy to clarify diagnosis and exclude hepatocellular carcinoma or metastasis, CE-US can often rule out malignancy.

FNH is known to contain centrally located fibrotic tissue (so called central scar), HCA tissue does not have a substantial fibrotic component and more closely resembles normal liver parenchyma. The current standard diagnostic workup includes MRI with adjunct role of CE-US. Larger lesions (> 35 mm) reduce diagnostic accuracy of CE-US [18]. FNH's fibrotic scar is stiffer than surrounding normal liver parenchyma, and this characteristic could be used for improving the diagnosis by focused elastography. Current methods (point Shear Wave Elastography, pSWE) use a US pulse released to a region of interest (ROI). Once there, it generates a perpendicular mechanical wave propagation through the liver tissue, and its velocity can be reliably measured. Such measurements can be also used to check stiffness of focal liver

abnormalities. pSWE of FNH and adenoma looks like a promising modality, and several preliminary studies suggest it may be beneficial in FLL diagnosis. To combine CE-US and local elastography appears to be an even more promising diagnostic step [19]. pSWE could improve CE-US diagnostic performance in equivocal cases in one US session. However, results for current small studies are dubious, and our study could not confirm the claimed diagnostic improvement. Interpretation of focal stiffness measurements should be done with caution [20].

Not all focal liver lesions are benign and management of malignant liver tumors varies substantially. Surgery will improve the survival of the patients if malignant lesions are not disseminated in the liver. Precise pre-operative method for their detection is therefore crucial. The exclusion of liver metastases in a patient with an already known extrahepatic tumour is nowadays suboptimal. Currently the reference method is computed tomography (CT), but metastases smaller than 1 cm can be missed or mistaken for another entity. The sensitivity and specificity of detecting metastases in the liver is low (for colorectal cancer metastases 82.1%, resp. 73.5%) [21]. CE-US presents good performance in differentiating benign versus malignant liver lesions, including metastasis. As our study confirmed, CE-US has a comparable sensitivity to CT for liver metastases detection in pancreatic cancer. We found that the main advantage of CE-US is in its capability to detect false-positive or clarify indeterminate CT results [22]. These results are promising and should be further explored in various screening programs.

In addition to diagnostic performance, the cost-effectiveness evaluations of healthcare interventions are important due to the rising costs of healthcare. Economic considerations together with clinical analyses provide the foundation for allocation of various resources. Several studies have shown that CE-US is a valuable cost-saving alternative compared to the current front-line diagnostic imaging. Expert MRI for FLL has better diagnostic results, but CE-US is cheaper. Studies exploring CE-US performance and cost consequences in various clinical situations, different countries, and healthcare settings calculated only direct diagnostic costs. Our study was the first one which included also treatment phase. It is of importance to also add a treatment phase to cost analysis studies and thus, combine diagnostic and treatment phases to evaluate the real impact of CE-US in the management of FLL.

One might assume that in the future, we can reasonably expect the availability of more specific microbubbles. The era of clinically available targeted CE-US may happen; as an example, bubbles coupled with antigens or receptors on their phospholipid surfaces that can attach to specific structures on tumor vasculature could be used. Such modified bubbles can improve tumor characterization. Targeted CE-US is not a surrogate for histological examination, but in some patients, we can avoid the need to perform a biopsy, and we can repeat measurements noninvasively,

check the tumor as a whole not only in the biopsy needle specimen, thus avoiding sampling error. The strict intravascular distribution of contrast agent is decisive for evaluating the antiangiogenic effects of new drugs. Furthermore, emergence of targeted CEUS allows not only more specific diagnostics but also targeted therapy. In addition, artificial intelligence (AI), particularly deep learning (DL) algorithms, is a significant yet emerging technological innovation in radiology. The power of DL devices lies in the capability to imitate neuronal cell activity, and they were developed to perform tasks specific for the human neocortex, such as learning and recognizing specific patterns of digital images. Also, AI-powered ultrasound is going to be more mature. It is approaching routine clinical application [23]. US examination includes operator-, patient-, and scanner-dependent parts [24]. In the future, AI can support human work, extend it, and also replace it. The projected impact on sonographers' work can be very profound [25]. But we are not there yet.

Furthermore, an area of future research involves the use of liver-specific microbubble contrast agent such as Sonazoid (perfluorobutane) [26]. Sonazoid is intracellular Kupffer phase agent and has limited reports yet. Kupffer phase starts at about 10 minutes and can last up to 120 min, allowing scanning of the whole liver in detail.

Current body of evidence is limited by small single-center studies of mostly retrospective design. Large multicenter studies would be helpful to clarify the usefulness of CEUS for indeterminate lesions on CT or MRI. Considering the difference of method of image acquisition and contrast material between CEUS and CT and MRI, combined assessment potentially improves accuracy.

Conclusion

In summary, there is still much to be investigated before we are able to effectively use CEUS in clinical practice. However, given the many endeavours by scientists, clinicians and radiologists all over the world, the future appears bright and hopeful.

BIBLIOGRAPHY

[1] L. Chiorean, V. Cantisani, C. Jenssen, P. Sidhu, U. Baum and C. Dietrich, "Focal masses in a noncirrhotic liver. The additional benefit of CEUS over baseline imaging," *Eur J Radiol,* pp. 1636-43, 84(9) Sep 2015.

[2] S. Wilson, P. Burns and Y. Kono, "Contrast/enhanced ultrasound of focal liver masses: a success story," *Ultrasound in Med & Biol,* vol. 46, no. 5, pp. 1059-1070, 2020.

[3] T. Albrecht, M. Blomley, L. Bolondi and et al, "Guidelines for the use of contrast agents in ultrasound," *Ultraschall Med,* pp. 249-256, 4 25 2004.

[4] C. Dietrich, C. Tana, C. Caraiani and Y. Dong, "Contrast enhanced ultrasound (CEUS) imaging of solid benign focal liver lesions," *Expert Review of Gastroenterology and Hepatology,* pp. 479-489, 5 12 2018.

[5] K. Seitz, D. Strobel, T. Bernatik, W. Blank, M. Friedrich-Rust, A. Herbay, C. Dietrich, H. Strunk, W. Kratzer and A. Schuler, "Contrast-Enhanced Ultrasound (CEUS) for the characterization of focal liver lesions - prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial).," *Ultraschall Med,* pp. 383-9, 4 Aug 30 2009.

[6] D. Cosgrove, "Ultrasound contrast enhancement of tumours," *Clin Radiol,* pp. Suppl 1 44-49, 51 Feb 1996.

[7] D. Wang, H. Jang and T. Kim, "Characterization of indeterminate liver lesions on CT and MRI with contrast-enhanced ultrasound: What is the evidence?," *Am J Radiology,* pp. 1295 - 1304, 2020: 214.

[8] C. Dietrich, C. Nolsoe, R. Barr, A. Berzigotti, P. Burns, V. Cantisani and et al, "Guidelines and good clinical practice recommendations for contrast-enhanced ultrasound (CEUS) in the liver - update 2020 WFUMB in cooperation with EFSUMB, AFSUMB, AIUM, and FLAUS," *Ultrasound in Med Biol,* pp. 2579 - 2604, Vol 46, No. 10 2020.

[9] EASL, "Clinical practice guidelines on the management of benign liver tumours," *Journal of Hepatology,* pp. 386-98, 2 65 2016.

[10] M. Broker, P. Taimr, M. de Vries, M. Braun, R. de Man, J. Ijzermans and R. Dwarkasing, "Performance of contrast-enhanced sonography versus MRI with liver-specific contrast agent for diagnosis of hepatocellular adenoma and focal nodular hyperplasia," *AJR Am J Roentgenol,* pp. 81-89, 214 (1) Jan 2020.

[11] H. Laumonier, H. Cailliez, C. Balabaud, L. Possenti, J. Zucman-Rossi, P. Bioulac-Sage and H. Trillaud, "Role of contrast-enhanced sonography in differentiation of subtypes of hepatocellular adenoma: correlation with MRI findings," *AJR Am J Roentgenol,* pp. 341-348, 199 (2) Aug 2012.

[12] P. Taimr, M. Broker, R. Dwarkasing, B. Hansen, R. de Knegt, R. de Man and J. IJzermans, "A Model-Based Prediction of the Probability of Hepatocellular Adenoma and Focal Nodular Hyperplasia Based on Characteristics on Contrast-Enhanced Ultrasound.," *Ultrasound Med Biol,* pp. 2144-2150, 10 Oct(43) 2017.

[13] J. Guy and M. Peters, "Liver disease in women: the influence of gender on epidemiology, natural history, and patients outcomes.," *Gastroenterol Hepatol (N.Y.),* pp. 633-9, 10 9 2013.

[14] M. Broker, Solid Benign Liver Tumours: Biological behaviour and management. PhD Thesis, Rotterdam: Erasmus Universiteit, the Netherlands, 2017.

[15] K. Daniels, J. Daugherty, J. Jones and W. Mosher, "Current contraceptive use and variation by selected characteristics among women aged 15-44: United States, 2011-2013.," *Natl Health Stat Report,* pp. 1-14, 86 2015.

[16] S. Dokmak and J. Belghiti, "Will weight loss become a future treatment of hepatocellular adenoma in obese patients?," *Liver Int,* pp. 2228-32, 35 (10) Oct 2015.

[17] M. Broker, M. Gaspersz, A. Klompenhouwer, B. Hansen, T. Terkivatan, P. Taimr, R. Dwarkasing, M. Thomeer, R. de Man and J. IJzermans, "Inflammatory and multiple hepatocellular adenoma are associated with a higher BMI.," *Eur J Gastroenterol Hepatol,* pp. 1183-1188, 10 Oct 29 2017.

[18] V. Roche, F. Pigneur, L. Tselikas, M. Roux, L. Baranes, M. Djabbari, C. Costentin, J. Caldarero, A. Laurent, A. Rahmouni and A. Luciani, "Differentiation of focal nodular hyperplasia from hepatocellular adenomas with low-mechanical-index contrast-enhanced sonography (CEUS): effect of size on diagnostic confidence.," *Eur Radiol,* pp. 186-195, 1 25 2015.

[19] A. Klompenhouwer, Benign Liver Tumors: From Diagnosis to Prognosis, PhD Thesis, Rotterdam: Erasmus University, the Netherlands, 2019.

[20] P. Taimr, A. Klompenhouwer, M. Thomeer, B. Hansen, J. IJzermans, R. de Man and R. de Knegt, "Can point shear wave elastography differentiate focal nodular hyperplasia from hepatocellular adenoma.," *J Clin Ultrasound,* pp. 380-385, 46 (6) Jul 2018.

[21] S. Choi, S. Kim, S. Park, K. Kim, J. Lee, S. Lee and M. Lee, "Diagnostic performance of CT, gadoxetate disodium-enhanced MRI, and PET/CT for the diagnosis of colorectal liver metastasis: Systematic review and meta-analysis.," *J Magn Reson Imaging,* pp. 1237-1250, 47(5) May 2018.

[22] P. Taimr, V. Jongerius, C. Pek, N. Krak, B. Hansen, H. Janssen, H. Metselaar and C. van Eijck, "Liver Contrast-Enhanced Ultrasound Improves Detection of Liver Metastases in Patients with Pancreatic or Periampullary Cancer.," *Ultrasound Med Biol,* pp. 3063-9, 12 Dec 41 2015.

[23] Z. Akkus, J. Cai, A. Boonrod, A. Zeinoddini, A. Weston, K. Philbrick and B. Erickson, "A Survey of Deep-Learning Applications in Ultrasound: Artificial Intelligence-Powered Ultrasound for Improving Clinical Workflow.," *J Am Coll Radiol,* pp. 1318-1328, 16(9 Pt B) Sep 2019.

[24] L. Zhou, J. Wang, S. Yu, G. Wu, Q. Wei, Y. Deng, X. Wu, X. Cui, X. Cui and C. Dietrich, "Artificial intelligence in medical imaging of the liver.," *World J Gastroenterol,* pp. 672-682, 25(6) 14 2019.

[25] A. Olthof, P. van Ooijen and M. Rezazade Mehrizi, "Promises of artificial intelligence in neuroradiology: a systematic technographic review," *Diagnostic Neuroradiology,* p. Epub ahead of print, 22 April 2020.

[26] R. Barr, P. Huang, Y. Luo, X. Xie, R. Zheng, K. Yan, X. Jing, Y. Luo, H. Xu, X. Fei and J. Lee, "Contrast-enhanced ultrasound imaging of the liver: a review of the clinical evidence for Sonovue and Sonazoid," *Abdominal Radiology,* 2020.