Acquisition and frequency spectroscopic evaluation of broadband clinical ultrasound raw data for liver cirrhosis and focal pathologies using neural networks for tissue and pathology differentiation

Protocol

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1. Summary

Background

Ultrasound examinations have become an integral part of everyday clinical practice. Ultrasound imaging impresses with a combination of availability, freedom from radiation and high diagnostic gain. So far, however, it is above all the diagnostic gain that must be critically questioned, as ultrasound examinations are strongly dependent on the examiner. Especially for the evaluation of ultrasound images, a wealth of experience is necessary. A more objective evaluation is offered by the technique of quantitative ultrasound (QUS). A quantitative evaluation of so-called RF data (radiofrequency data) enables a more accurate diagnosis that is independent of the assessor. The gain in information is similar to the change from black-and-white television to color television. Physically, this is based on the individual, frequency-dependent sound reflection of tissues and pathologies depending on their biomechanical properties. This makes it possible, for example, to automate the segmentation of ultrasound images or the early detection of hepatic steatosis. Previous systems are based on narrowband piezo transducers, which is why a broadband analysis of tissue properties in the clinical setting has not yet been carried out. The approach is thus like promising ex-vivo studies, such as Gare et al., 2022, Nguyen et al., 2021 and Gangeh et al., 2014 .

Goal

Within the framework of basic research, multicenter *prospective*, anonymized, broadband raw ultrasound data are to be collected for the first time in a common database. The basis for this database is the cooperation of several German centers (previously planned: University Hospital Dresden, Municipal Hospital Dresden, University Hospital Leipzig, University Hospital Halle). These data will be used to evaluate a trained neural network, which can classify liver fibrosis based on RF data.

To collect the necessary amounts of data, further centers are to be included in the course of the process. Thus, the study builds on previous analyses from *retrospective* data from the University Hospital Dresden (ethics application BO-EK-534122022) and is intended to test some of the promising preliminary results in a prospective approach.

Design

The study is designed as a prospective, multicenter, experimental study. Female and male patients will be included who will receive a sonographic examination with reliable ground truth (depending on the local standard procedures of the center e.g. biopsy, contrast-enhanced ultrasound [CEUS], elastography, CT, MRI). In order not to create any additional effort, only patients with planned further clinical examinations are included. The data will then be used for validation by the already trained neural networks.
The prerequisites for participation are existing consent, the age of majority and no minor interventions on the liver within the last 14 days or within the last 14 days. Exclusion from major intervention within the last 6 months (see also 4. Test).

2. Objective of the study

The aim of the study is to collect liver-specific ultrasound raw data and images, collect them in the form of a multicenter, anonymized, local database and subsequently evaluate them spectroscopes using methods like convolutional neural networks (CNN). The networks were trained on retrospective data from a separate ethics application (BO-EK-534122022) and are to be validated in these data primarily, but not exclusively. Should a sufficient amount of data arise to enable sufficient training, the use of the data for the training of the Networks would also be a goal.

General objective

Demonstrate that frequency spectroscopic analysis of raw ultrasound (RF) data enables the detection, classification, and differentiation of different tissue-specific entities.

Initial more specific hypotheses:

1. The evaluation of RF data of the liver by neural networks with liver elastography results as a reference standard enables the detection and classification of degrees of steatosis, fibrosis and cirrhosis.
2. Neural networks trained on RF data are better than networks trained on B-scans at detecting degrees of steatosis, fibrosis, and cirrhosis as measured in AUC.
3. The diagnostic certainty of the degree of steatosis, fibrosis and cirrhosis of a neural network trained on RF data depends on the bandwidth of the US signal provided
4. The evaluation of RF data of the liver by neural networks with histology results as a reference standard enables the detection and classification of hepatic cavities.
5. The evaluation of RF data of the liver by neural networks with results of contrast ultrasonography as a reference standard enables the detection and classification of hepatic cavities.
6. Neural networks trained on RF data are better than networks trained on B-scans in classifying liver cavities.

3. Study design

The study is designed as a prospective, multicenter, experimental study. Female and male patients undergoing sonographic examination with biopsy, CEUS or elastography will be included. It is important to ensure that the corresponding examinations would also be carried out independently of the study so as not to create any additional effort for the patient. The only difference is the additional systemic acquisition of raw ultrasound data, which is not always stored in conventional examinations.

Type of study

- prospective, multicenter, experimental study

Sample size planning

For the validation of the networks, a sample size of at least 200 patients is targeted. After completion of the data collection, each degree of fibrosis should be present about 20 times in order to enable a valid performance of the network for each degree of fibrosis. If this is not achieved, data collection will continue for 100 additional patients and then the distribution will be reviewed again. This is repeated until the target minimum number is reached. For focal

lesions we plan to include 50 patients per lesion. If this criterion is not met, data acquisition continuous.

4. Test Method

Study population

Female and male subjects over 18 years of age who are undergoing biopsy, CEUS, or elastography as part of an ultrasound scan.

Inclusion Criteria

- Age over 18 years
- Subject's capacity to give consent
- Signed declaration of consent by the subject

Exclusion criteria

- minor intervention (e.g. biopsy) performed less than a week ago in the same area
- CEUS carried out less than a day ago
- Major intervention on the liver (e.g. resection) in the history

Course of study

The required RF data is recorded shortly before the actual investigations, which provide us with the required ground truth. The data acquisition is carried out with approved devices from everyday clinical use. Specifically, Clarius' C3HD3 US handheld models are used as a low-frequency abdominal transducer and Clarius' L15HD3 as a high-frequency linear transducer. The data from the two transducers are combined in the evaluation to simulate broadband recordings. In the so-called RF mode, both B-scans and ultrasonic raw data are recorded in the form of RF data. The raw data is only recorded within a predefined region of interest (ROI).
The data is then temporarily stored locally on a mobile device as an interface to the ultrasound device and manually copied from there to a local network drive of the University Hospital Dresden. The mobile devices are not connected to the Internet and are protected from unauthorized access by a password. Access to the network drive is only permitted to persons named in the ethics application. On the local drive, the patient age, patient gender and the diagnosis from the doctor's letter are then assigned to the images. Subsequently, this combined data set is anonymized and stored for evaluation. The test persons are assigned a number that does not allow any conclusions to be drawn about their identity and is only used for assignment within the anonymous data set.
Additional centers will record their data in the same form. Once anonymization and local storage have been completed, the data is manually inserted into the Dresden dataset via local data carriers.

Risks

Due to the ultrasound systems used, no particular risks are to be expected. All devices used in the study are certified according to European safety standards for electrical equipment and approved for clinical use. The examinations carried out as part of the study are similar to normal clinical ultrasound examinations. Since these are carried out anyway, an additional

burden for the patients is inherently excluded. In addition, the ultrasound examination is considered non-ionizing and neither physically nor psychologically stressful. The total additional time required for the subject is approximately 5 minutes (2.5 minutes per ultrasound transducer).

Effect/Benefits

The raw data collected by the study can provide much more information about the examined tissue than the B-scans previously used for evaluation. In addition to information on reflected sound intensity, this RF data also contains frequency information. This makes it possible to create new methods for the classification and segmentation of different tissues or entities in ultrasound. In the future, this could replace examinations such as biopsies, CEUS and elastography with classic ultrasound examinations. This would spare patients physical strain and risks and make the everyday life of the treating physicians easier. Furthermore, it is possible to color-code different tissues in the ultrasound image, which would make them easier to differentiate. This would increase the accuracy of ultrasound scans, especially for less experienced examiners.
The anonymized raw data sets of several clinics are to be merged into a public database. This will enable further follow-up studies based on the data collected.

Abandonment Criteria

The study will be stopped immediately at the request of the subject. At the same time, no events are to be expected from the study itself that would cause an abortion. Subjects will be informed that they can terminate their participation in the study without giving reasons and without any disadvantages.

5. Ethical and legal aspects

The planning, implementation and exploitation of the project and the project results shall be carried out in accordance with the relevant ethical and scientific standards. The applicants thus commit themselves to comply with the requirements of the Memorandum on Safeguarding Good Scientific Practice of the German Research Foundation (DFG), the Declaration of Helsinki and the State and Federal Data Protection Acts, as well as the General Data Protection Regulation of the European Union (EU GDPR). In addition, the clinically active colleagues involved follow the professional regulations for physicians of the responsible State Medical Association in the current versions. The curriculum was submitted to the Ethics Committee of the University Hospital Dresden for consultation before the start of the study. The names of the test persons and all other confidential information are subject to the medical confidentiality of the treating physicians and the provisions of the General Data Protection Regulation or the Federal Data Protection Laws (GDPR or BDSG).
The planned study is not a study according to MPG or AMG. Before participating in the study, interested participants will be informed in detail about the study by the study staff in writing and orally and will be given the opportunity to ask questions about the study. With the study information, participants will receive the contact details of a study staff member so that they can contact them at any time. Participants will be informed that they can terminate their participation in the study without giving any reason and without any disadvantages.

The study is insured for up to €10,000,000 through public liability insurance. The corresponding proof from Marsh Medical Consulting GmbH is enclosed with the application.

6. Privacy

The procedure was coordinated with the data protection officer of the University Hospital (see DSB consultation result). No concerns were raised with regard to data protection.

Once enrolled in the study, subjects will receive a study participation ID that does not contain any personal identifying information. Since the subject's identity is no longer relevant to the study after the combination of ultrasound data and the clinical parameters such as age, gender and the diagnosis from the doctor's letter, the name of the subject is not noted in connection with the study ID or the data collected. Only the information sheets contain the names of the test subjects. These are only kept in paper form and stored in a lockable filing cabinet in the EKFZ together with other study-related forms.

All image data recorded during the study will be stored anonymously in local network servers of the University Hospital Dresden. The data collected during the study will be used exclusively for the purposes indicated and will not be shared with third parties. However, the local raw data will be stored for a maximum of ten years until the end of the evaluation, in accordance with the retention period specified by the German Research Foundation (DFG) or in accordance with the legally prescribed archiving period for clinical studies. After the end of the retention period, the files are deleted from all data carriers as well as data sheets (questionnaires, declarations of consent, etc.) are destroyed via the clinic's internal data protection-compliant document destruction.

All project staff and partners involved are subject to the European General Data Protection Regulation.

7. Planned recovery

The central benefit of the study is the generation of a raw clinical ultrasound data set and the testing of new examination methods, especially on the basis of artificial intelligence. The plan is to use the data in a medical doctoral thesis and to create a public ultrasound raw database. In addition, the results will be presented at recognized national and international conferences. The results will be published in an internationally recognized journal.

8. References

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