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Development of a new super-resolution ultrasound test to find cancerous sentinel lymph nodes in patients with breast cancer

Submission date 26/03/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 03/08/2021	**Overall study status** Completed	
Last Edited 29/04/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Thousands of people are told that they have breast cancer every year in the UK and most will need an operation to remove the cancer. As well as removing the cancer in the breast, they are advised to have some or all of their lymph nodes removed from the armpit. As most people have early-stage breast cancer, only 3/10 will have cancer deposits in the lymph nodes. This means that many breast cancer patients are having unnecessary surgery on the armpit. The risks of removing lymph nodes from the armpit include infection, bleeding and fluid collections as well as problems like arm swelling, loss of feeling or sometimes pain down the arm. That could last for many years. A new more precise ultrasound test could replace armpit surgery for many breast cancer patients.

The aim of this study is to develop a new ultrasound test to replace armpit surgery and the idea came from front-line breast cancer doctors and nurses together with patients living with problems caused by armpit surgery. The new ultrasound test builds on technology developed at Imperial College London and studies pioneered at Maidstone Hospital in Kent using ultrasound contrast (microbubbles) to find sentinel lymph nodes. At the end of the study, the plan is to have a new contrast ultrasound test (made up of software and equipment) that can be used with ultrasound machines in the breast clinic for armpit scanning.

Who can participate?

Women aged between 18 and 80 years who have recently been diagnosed with breast cancer with a plan for surgery as the first treatment

What does the study involve?

Breast cancer treatment will happen normally. The only difference is that participants will also have the new ultrasound procedure using microbubbles to find sentinel lymph nodes before their operation. Participants will need to come back for an extra visit to the breast unit's ultrasound department to have the new ultrasound test. A consultant breast radiologist will perform the new ultrasound test and one of the biomedical engineers from Imperial College will also be present for the procedure. A member of the London IVD Group from Imperial College may also be present as their job in the research is to make sure that the new test is comfortable

and user-friendly. The test should take about 45 minutes. The radiology team will insert a cannula (small tube) into a vein in the arm. They will then use some local anaesthetic to numb an area at the edge of the nipple skin and inject a small amount of ultrasound contrast. They will massage the area to encourage the contrast to move into the breast tissue fluid channels. The ultrasound machine will be used to follow the contrast to the sentinel lymph node in the armpit. They will then switch on the ultrasound super-resolution and collect images of the sentinel lymph nodes for about 2 minutes. The radiologist will then inject ultrasound contrast into the cannula and repeat the ultrasound of the sentinel lymph nodes using super-resolution. They will collect images again for about 2 minutes. They may also take a biopsy from the sentinel lymph node and leave a small titanium clip to mark the biopsied lymph node. After the test, participants will be asked to complete a satisfaction questionnaire. Their breast and armpit operation will then proceed as normal as scheduled by their doctors.

What are the possible benefits and risks of taking part?
There is no direct benefit to participants. However, this study could have long-term benefits for future patients with breast cancer. Participants will need to come back to the breast unit for an extra visit. Injecting microbubbles into the breast and bloodstream is safe but there are some uncommon (1/1000 to 1/100) side effects such as headache, dizziness, tingling of the skin, a funny taste in the mouth, skin flushing, sickness, abdominal pain, skin rash, chest discomfort, feeling hot and skin redness at the site of the injection. Rare (1/10,000 to 1/1000) side effects include allergic reaction, blurred vision, low blood pressure, itching of the skin, back pain, chest pain and fatigue.

Where is the study run from?
1. Maidstone and Tunbridge Wells NHS Trust (UK)
2. Imperial College Healthcare NHS Trust (UK)

When is the study starting and how long is it expected to run for?
October 2020 to April 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Miss Karina Cox
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
293812

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 293812, CPMS 50268

Study information

Scientific Title
Detection of metastatic axillary sentinel lymph nodes using ultrafast, super-resolution, dual-contrast enhanced ultrasound imaging in patients with breast cancer

Acronym
LiSENUS

Study objectives
The project aims to develop a prototype CEUS imaging system, built initially around research system hardware (Verasonics, Kirkland, USA), with new software, data processing algorithms, a 3D data acquisition rig and radiology protocols/patient pathways for ultrafast, super-resolution dual contrast-enhanced ultrasound imaging of armpit sentinel nodes to allow the detection and quantification of metastases, validate it for clinical use and conduct a small proof of principle clinical trial to demonstrate usefulness as a diagnostic test.

The proposed final product will be a combination of software and hardware that can act as a ‘bolt-on’ to commercially available ultrasound machines used for imaging the breast and armpit in clinic.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design

Dual-centre study to develop a prototype super-resolution contrast-enhanced ultrasound (CEUS) imaging system and demonstrate its usefulness as a diagnostic test

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Identification of malignant axillary lymph nodes in patients with breast cancer

Interventions
Work Plan 1
Work on test phantoms:
While the current image data acquisition using the Verasonics research ultrasound machine is ultrafast (>10 kfps), the image formation and super-resolution processing have to be performed via slow offline processing due to the large amount of data acquired. Furthermore, a rig for 3D data acquisition with a clinical imaging transducer probe that is suitable for breast and armpit scanning will need to be designed and evaluated. Initially, the GE L3-12-D linear array probe (General Electric, Boston, MA) will be trialled. However, other different commercially available transducer probes may also be assessed to find the optimum probe for the acquisition rig.
Initial work will be performed using tissue-mimicking phantoms with embedded circular structures simulating human armpit geometry and structure. A 3D data acquisition rig suitable for scanning the human armpit will be developed.
Such a rig will allow: 1) freehand scanning by the operator to localize sentinel nodes; 2) an electromagnetic device connected to track the probe; 3) the probe finally being scanned across the armpit while ultrafast data is acquired. An optimal balance between the numbers of 2D scan planes and the total time required will be sought. Imaging methodology including 2D acquisition, image reconstruction, and super-resolution post-processing will be evaluated.

Work with breast cancer patients:
Optimisation of the system will involve 20 newly diagnosed breast cancer patients (10 from MTW and 10 from IHC) all with surgery as their planned first treatment.
The CEUS procedure will not provide any information that will contribute to their treatment plan and they will continue with standard care.

Procedure:
1. Eligible patients will be identified in the weekly breast MDT meeting a given a unique study number.
2. After consent, a radiologist will perform the CEUS procedure: using an aseptic technique, a

cannula is sited into a peripheral vein and local anaesthetic injected at the edge of the nipple-areolar complex in the upper outer position.
3. Two vials of the contrast agent are each mixed with 5 ml of normal saline. Up to 2.5 ml is injected under the skin of the breast at the site of the local anaesthetic and up to 5 ml of contrast agent is injected as a slow infusion. The breast is gently massaged to encourage the contrast to be taken up by the lymphatic tissue fluid channels.
4. The breast and armpit are scanned using existing ultrasound technology to identify the position of the tumour and locate the contrast agent before tracking the microbubbles to the armpit sentinel nodes. Super-resolution images of the sentinel nodes at multiple planes will be acquired through a rig with a probe tracking system (at least 2 min) and stored for offline analysis. The optimal configuration number of scanning planes, contrast pulse sequences and multi-angle compounding for imaging blood and lymph flow as well as the optimal microbubble contrast infusion rate will be investigated. Patients will continue with breast and axillary surgery, as is the standard of care.
5. Histopathological information regarding the excised breast cancer and lymph node metastatic involvement will be collected.

Data processing:
The existing codes will be translated to codes to be executed on a graphics processing unit (GPU) for a) beamforming; b) bubble detection and localisation; c) post beamforming signal processing; and d) motion correction. In house beamforming code has already been developed with experience in code transfer to GPU based processing.
Microbubble localisation, signal processing/filtering and motion correction codes have also been developed. These codes will be optimised for a higher-end GPU fast/real-time imaging. The goal is to achieve real-time imaging (>20 fps) for vessel tracking and display the accumulated super-resolution image with real-time updates (>20 fps) for lymph node imaging. A graphic user interface, suitable for clinical use, will be developed.

Work Plan 2
The prototype CEUS system will be compared with the existing UK standard preoperative armpit B-mode ultrasound and the reference (gold) standard for detecting armpit lymph node metastases (surgery and pathological analysis) in a pilot study.
The results of the B-mode armpit ultrasound will be used to guide decisions regarding armpit surgery, as is the UK standard of care; 1) if abnormal lymph nodes are seen and metastases proved by needle biopsy the recommendation is for all armpit lymph nodes to be removed (ALND); 2) if the B-mode ultrasound is normal, only sentinel nodes are removed at the first operation with subsequent ALND if 3 or more sentinel nodes contain macrometastatic (>2 mm) deposits of cancer or 1-2 SLN contain macrometastases and the patient is not suitable for axillary conservation (7,8).

A chosen sample size of 40 newly diagnosed breast cancer patients is based on the practical considerations of recruitment.

The multidisciplinary team will be blinded to the CEUS results and they will not be used to guide treatment decisions. This will prevent overestimation of test accuracy with all lymph nodes removed in CEUS test positives.

Procedure:
1. Eligible patients will be identified in the weekly breast MDT meeting and given a unique identifying study number.
2. After consent, a radiologist (blinded to the patient results discussed at the MDT meeting) will perform a B-mode axillary ultrasound and be asked to report one of three possible outcomes

based on B-mode imaging criteria alone: A. No lymph node metastases, B. 1-2 lymph node metastases, C. 3 or more lymph nodes containing metastases.
3. A second radiologist (blinded to the results of the B-mode axillary ultrasound and the patient results discussed at the MDT meeting) will then perform the CEUS procedure: Using an aseptic technique, a cannula is sited into a peripheral vein and local anaesthetic injected at the edge of the nipple-areolar complex in the upper outer position.
4. Two vials of the contrast agent are each mixed with 5 ml of normal saline. Up to 2.5 ml is injected under the skin of the breast at the site of the local anaesthetic and up to 5 ml of contrast agent is injected as a slow infusion. The breast is gently massaged to encourage the contrast to be taken up by the lymphatic tissue fluid channels.
5. The breast and armpit are scanned using existing ultrasound technology to identify the position of the tumour and locate the contrast agent before tracking the microbubbles to the armpit sentinel nodes. Super-resolution images of the sentinel nodes at multiple planes will be acquired through a rig with a probe tracking system (at least 2 min) and stored for offline analysis. The first draining sentinel node is core biopsied and a small marker clip is left to identify the biopsied sentinel node.
6. The radiologist will report one of three possible outcomes based on imaging criteria alone: A. no lymph node metastases, B. 1-2 lymph node metastases, C. 3 or more lymph nodes containing metastases.
7. Histopathological information regarding the excised breast cancer and lymph node metastatic involvement will be collected.
8. At the post-surgical MDT meeting, the results of the CEUS sentinel lymph node biopsy will be un-blinded to the clinical team as this may affect decisions regarding adjuvant treatment if the biopsy contained malignant cells. The patient will also be told the results of the CEUS sentinel lymph node biopsy at their post-surgical clinic visit.
9. Concordance between CEUS and true pathology (armpit surgery) will be analysed by calculating the sensitivity, specificity, positive predictive value and negative predictive value. Concordance between B-mode and CEUS will also be analysed.
10. Time-to-event methods (Kaplan-Meier type graphs, median times) will be used to summarise and report the first three outcomes where the events of interest will be ‘visualisation of lymphatic vessels’, ‘visualisation of sentinel nodes’ and ‘core biopsy and clip sentinel nodes’. The proportion of sentinel nodes successfully visualized will be reported using descriptive statistics.

Intervention Type
Device

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
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Primary outcome measure
1. The functional ability of the prototype super-resolution CEUS system measured using tissue phantoms during the first 6 months of the study
2. Time to event measures of the prototype super-resolution CEUS system: visualisation of lymphatics, visualisation of SLN in axilla and core biopsy and clip SLN recorded for each clinical procedure
3. Diagnostic performance assessed by calculating the sensitivity, specificity, positive predictive value and negative predictive value of the prototype super-resolution system as a test to identify sentinel lymph node metastases compared to the reference standard of axillary surgery.

The statistical report will be provided by month 32 of the study.
4. The inter-rater reliability of imaging specialists measured with an observer study conducted between months 28 and 36 of the study

Secondary outcome measures
1. Adverse events measured with patient questionnaires completed immediately after the super-resolution CEUS test and clinician questionnaires completed on the day of surgical treatment (approximately 2-3 weeks after the super-resolution CEUS test)
2. Feedback on perceived usability collected through validated scales (UMUX, System Usability Scale - SUS, NET promoter score) from imaging specialists after each super-resolution CEUS test
3. Patient and clinical satisfaction measured with patient and imaging specialist questionnaires completed immediately after each super-resolution CEUS test
4. Stakeholder analysis and pathway mapping conducted using a WHO stakeholder analysis framework and completed by month 30
5. Health economics report produced from information from the stakeholder analysis and clinical studies by month 30

Overall study start date
05/10/2020

Completion date
04/04/2023

Eligibility

Key inclusion criteria
1. Provision of written informed consent
2. Histologically confirmed invasive carcinoma of the breast with planned primary surgical treatment
3. Female aged 18 to 80 years
4. In the Investigator’s opinion, adhering to the trial recommendations and governance

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Female

Target number of participants
60 in total (20 work plan 1 and 40 work plan 2)

Key exclusion criteria
1. Previous ipsilateral breast cancer treated with radiotherapy or chemotherapy
2. Participant who is pregnant, lactating or planning pregnancy during the course of the study
3. Allergy to ultrasound contrast
4. Cannot provide consent
5. Inflammatory or locally advanced breast cancer
6. Patients with right to left cardiac shunts
7. Severe pulmonary hypertension
8. Adult respiratory distress syndrome
9. Uncontrolled hypertension
10. Heart failure
11. Renal failure
12. Recent thromboembolism
13. Hypercoagulation disorder

Date of first enrolment
26/08/2021

Date of final enrolment
04/04/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Maidstone Hospital
Maidstone and Tunbridge Wells NHS Trust
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Sponsor information

Organisation
Maidstone and Tunbridge Wells NHS Trust

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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/02yq33n72

Funder(s)

Funder type
Government

Funder Name
Invention for Innovation Programme

Alternative Name(s)
NIHR Invention for Innovation Programme, i4i

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. The Trial Management Group supports the sharing of data with other researchers wishing to undertake additional analyses and will consider all formal requests for sharing data within this research. Once agreed, a data-sharing agreement will be established between the Sponsor and recipient describing the conditions for data release and requirements for transfer, storage and publication to ensure that relevant intellectual property and the identity of individual trial participants are protected.

Intention to publish date
05/10/2024

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from co-chief investigator Karina Cox (karina.cox@nhs.net). Anonymised data regarding time to event measures, diagnostic accuracy, inter-rater reliability, adverse events, usability, patient and clinician satisfaction and health economics will be available from the end of the trial for 5 years. All reasonable requests for data will be assessed by the co-investigators and funder. Specific data requests regarding the high-resolution contrast ultrasound system are likely to be subject to intellectual property regulations and will be assessed by the funder and Imperial Innovations.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Work package 1 version 1	01/03/2021	02/11/2021	No	Yes
Participant information sheet	Work package 2 version 1	02/03/2021	02/11/2021	No	Yes