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In patients with breast cancer, can imaging specialists be taught to use an advanced ultrasound technique to successfully find cancer deposits in armpit sentinel lymph nodes with microbubbles injected into the breast?

Submission date	**Recruitment status**	[X] Prospectively registered
05/03/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
30/04/2020	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
18/12/2020	Cancer	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Around 46,000 people are diagnosed with invasive breast cancer every year in the UK. As well as removing the tumour in the breast, they are advised to have some or all of their lymph nodes removed from the armpit. As most patients have early stage breast cancer, about 70% will not have cancer deposits in the lymph nodes. Therefore, many patients risk the potential complications from armpit surgery such as infection, bleeding and fluid collection as well as arm swelling, loss of sensation or sometimes pain down the arm, for no benefit. There is already a lot of effort to reduce armpit surgery and better use of ultrasound may help to identify patients who don't need this surgery at all. We are planning to train specialists from five hospitals to perform a special ultrasound technique, which uses microbubbles injected into the breast that can be seen with the ultrasound and followed into the armpit to find the sentinel (or key) lymph nodes. The specialist can then take a needle biopsy to see if the sentinel lymph nodes contain cancer deposits. It is important to prove that local specialists can easily and reliably perform the microbubbles procedure in the breast clinic. If this research is successful, the plan is to run a larger study to make sure that replacing armpit surgery with the microbubbles procedure is safe and doesn't increase the risk of the cancer coming back more than the present surgery to the armpit.

Who can participate?

Any woman over the age of 18 who has just found out that they have early breast cancer with normal appearing armpit lymph nodes on the conventional ultrasound or a benign (non-cancerous) biopsy of abnormal armpit lymph nodes seen on the conventional ultrasound with surgery planned as their first treatment.

What does the study involve?

Women taking part will need to come back to the breast unit's ultrasound department to have

the microbubbles procedure. The imaging specialist will use some local anaesthetic to numb the area and will inject a small amount of microbubbles into the breast at the edge of the nipple. They will then massage the area to encourage the microbubbles to absorb into the breast. The ultrasound machine will be used to track the microbubbles as they pass through the breast to the sentinel lymph node in the armpit. The imaging specialist will use a bit more local anaesthetic in the armpit and then use a standard biopsy needle to take biopsies of the sentinel lymph node. They will also leave a small marker clip to show which lymph node has been biopsied.
Women who have had the procedure will return to see their surgical team about a week after the microbubbles procedure for the results of the sentinel lymph node biopsy to plan what type of operation they will have in the armpit. At that appointment, women will be asked to fill out a satisfaction questionnaire about the microbubbles procedure.
The breast and armpit operation will proceed as normal. Women will be asked to fill out a satisfaction questionnaire about the armpit surgery and that marks the end of their involvement with the study. The other recommended treatments for the breast cancer will continue as normal.

What are the possible benefits and risks of participating?
If the sentinel lymph node biopsy does not show cancerous cells, then it is unlikely that armpit surgery will find a significant number of cancerous lymph nodes that have been missed by both the conventional and microbubble ultrasound tests. If a cancerous deposit is found in the sentinel lymph node with the microbubbles biopsy then this information is often useful to help make decisions about treatment quickly after diagnosis. For instance, the woman and her doctors may decide to change their first treatment from surgery to chemotherapy. If a woman is having a mastectomy, finding a cancerous deposit in the sentinel lymph node may mean that radiotherapy is recommended after the mastectomy. Radiotherapy can negatively affect the final cosmetic appearance after a reconstruction so it may be better to have the reconstruction later to get the best long-term result.
The microbubbles biopsy procedure is safe and very few women experience irritation or allergy after the microbubbles are injected and there have been few problems with bleeding after the biopsy (less than 1/100).

Where is the study run from?
The study is run from Maidstone and Tunbridge Wells NHS Trust in Kent, England and Warwick Medical School Clinical Trials Unit.

When is the study starting and how long is it expected to run for?
The study is due to start in October 2020 and will run for 2 years.

Who is funding the study?
The charity Breast Cancer Now is funding the study.

Who is the main contact?
Miss Karina Cox, consultant breast surgeon at Maidstone and Tunbridge Wells NHS Trust
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Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
2020-000819-67

IRAS number
274252

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
MTW_2020_KC01, IRAS 274252

Study information

Scientific Title
Multicentre phase II trial to assess technical feasibility and diagnostic accuracy of intradermal microbubbles and contrast-enhanced ultrasound to identify sentinel lymph node metastases in breast cancer patients compared to axillary surgery following training and mentorship of imaging specialists

Acronym
SENTINUS

Study objectives
1. Technical feasibility - To determine whether 10 experienced imaging specialists (4 with previous exposure to the technique and 6 who are naïve to the procedure) in 5 UK Breast Centres can be trained to consistently identify, core biopsy and clip mark axillary sentinel lymph nodes in patients with breast cancer
2. Diagnostic accuracy - To determine the overall diagnostic accuracy of a CEUS sentinel lymph node core biopsy as a test to identify sentinel lymph node metastases as compared to the reference standard of axillary surgery

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Multicentre phase II interventional non-randomized incorporating a training and mentorship programme

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Breast cancer

Interventions
Patient Intervention:
1. Following written informed consent and registration, a contrast-enhanced ultrasound and biopsy of axillary sentinel lymph nodes (with clip marking) will be undertaken.

Research study: Aseptic technique. 1% lignocaine is injected subcutaneously into the sub areola region. The contrast agent - “sonovue” is mixed with 2.5mls of water and 1mls is injected intra-dermally at the site of the local anaesthetic. The breast is gently massaged to encourage the contrast to be taken up by the lymphatics. The axilla is scanned and the contrast software package used on the ultrasound machine allows visualisation of the contrast agent into the axilla. The first draining lymph node is highlighted and biopsied using a 14G conventional core biopsy needle. A marker clip is placed into the lymph node to identify which node has been biopsied.
The patients will receive a standard aftercare leaflet about axillary nodal examination and biopsy.

2. 1 week later, the patient will return to the breast clinic to receive the results of the sentinel lymph node biopsy from their surgical team and fill out a satisfaction questionnaire about the axillary biopsy procedure.
3. Less than 31 days later, breast surgery will be undertaken as standard of care together with axillary surgery as decided by the treating clinicians in the multi-disciplinary team and the patient based on the result of the sentinel lymph node biopsy.
4. The patient will return to the breast clinic 1-2 weeks after surgery to receive the results of the operation from their surgical team and will fill out a satisfaction questionnaire about their axillary surgery. This marks the end of their involvement with the trial.

Training and Mentorship Programme:
Imaging specialists will be recruited from 5 Breast Cancer Units within the UK. Two units will have prior experience of using intradermal microbubbles and CEUS to identify and biopsy sentinel lymph nodes in patients with early breast cancer and 3 units will be naïve to the technique. Each unit will put forward 2 imaging specialists to take part in the study, therefore 10 in total.
For those units without prior experience of intradermal microbubbles, if necessary, their existing ultrasound machines will be upgraded to allow contrast studies.
Participating imaging specialists will attend an all-day training session at Maidstone Hospital, Kent. They will have access to video tutorials and written information. Two radiologists, experienced in using the technique, will provide mentorship either by telephone or site visits if necessary.
During the trial period, each unit will also prospectively audit their malignant lymph node detection rate with conventional B-mode axillary ultrasound and biopsy.

Intervention Type
Procedure/Surgery

Primary outcome measure
1. Technical feasibility will be assessed by 75% of imaging specialists achieving; >85% visualization of tumour draining axillary SLN, >80% successful core biopsy (LN tissue retrieved) rate and >80% concordance with SLN identified surgically with SLNE.
2. Diagnostic performance will be assessed by calculating the overall pooled sensitivity, specificity, positive predictive value, negative predictive value of CEUS SLN core biopsy as a test to identify SLN metastases as compared to axillary surgery and the prevalence of LN metastases. An overall sensitivity >50% will be considered acceptable.

Secondary outcome measures
Measured using case report forms completed at the time of procedure:
1. Time taken to perform each CEUS SLN core biopsy procedure

2. Total volume of axillary disease at the end of primary surgical treatment for each patient
3. Bleeding complications (CEUS SLN core biopsy and subsequent axillary surgery)
4. Infective complications (CEUS SLN core biopsy and subsequent axillary surgery)
5. Pain/ sensory disturbance (CEUS SLN core biopsy and subsequent axillary surgery)
6. Patient satisfaction (CEUS SLN core biopsy and subsequent axillary surgery)
7. Prospective audit of each unit's detection rate of LN metastases with grey-scale axillary ultrasound

Overall study start date
02/02/2020

Completion date
04/04/2022

Eligibility

Key inclusion criteria
1. Newly diagnosed early invasive carcinoma of the breast with a normal B-mode axillary ultrasound or benign biopsy of indeterminate lymph nodes
2. Surgery as first planned treatment
3. Participant is willing and able to give informed consent for participation in the trial
4. Female, aged 18 years or above
5. In the Investigator's opinion, adhering to the trial recommendations and governance

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
250

Key exclusion criteria
1. Previous ipsilateral axillary surgery or ipsilateral breast cancer surgery/ radiotherapy
2. Female participant who is pregnant, lactating or planning pregnancy during the course of the trial
3. Contraindication to contrast
4. Patient cannot provide consent
5. Inflammatory or locally advanced breast cancer
6. Metastatic breast cancer
7. Inability to raise ipsilateral arm above head
8. Multiple medical co-morbidities (ASA 4 or above)

Date of first enrolment
05/10/2020

Date of final enrolment
04/03/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Maidstone Hospital
Maidstone and Tunbridge Wells NHS Trust
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
St James Hospital
Beckett St.
Leeds
United Kingdom
LS9 7TF

Study participating centre
St Bartholomew's Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Bristol Royal Infirmary
Marlborough Street
Bristol
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BS2 8HW

Sponsor information

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Sponsor type
Hospital/treatment centre

Website
https://www.mtw.nhs.uk

ROR
https://ror.org/02yq33n72

Funder(s)

Funder type
Charity

Funder Name
Breast Cancer Now

Alternative Name(s)
BCN

Funding Body Type

Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The researchers will work with all stakeholders (the Sponsor, university, Principal investigators, and our patient advisory groups) to generate dissemination materials and to optimise the engagement of relevant audiences.
Dissemination will include presentations at national and international conferences and publication in peer review journals. In addition, a patient-specific results summary will be produced with our patient representative's help and disseminated through their contacts, other patient representatives and patient group websites including ICPV.
The Trial Management Group will consider all reasonable formal requests for sharing data collected within this research. Once agreed, a data-sharing agreement will be set up by the Sponsors that describe the conditions for data release and requirements for transfer, storage and publication.

Intention to publish date
11/11/2022

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version v3.0	19/03/2020	30/04/2020	No	Yes
Participant information sheet	version v1.0	20/02/2020	30/04/2020	No	Yes
Protocol file	version v2.0	23/03/2020	30/04/2020	No	No