Maidstone and Tunbridge Wells NHS Trust

Imaging Specialist Participant Information Sheet

Title of Project: SENTINUS: Technical feasibility and diagnostic accuracy of intradermal microbubbles and contrast enhanced ultrasound to identify sentinel lymph node metastases in breast cancer patients following training and mentorship of imaging specialists

Name of Chief Investigator: Karina Cox (Consultant Breast Surgeon).

Invitation

We'd like to invite you to take part in our pilot study to train imaging specialists to use intradermal microbubbles and contrast enhanced ultrasound (CEUS) to find and biopsy sentinel lymph nodes in patients with early breast cancer. We also want to look at the diagnostic accuracy of the procedure as a test to find sentinel lymph node metastases.

Summary

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.

Over the last decade, a system has been developed which uses intradermally injected microbubble contrast agent and CEUS to dynamically image breast lymphatics and follow the vessels to sentinel nodes. Under direct vision, the sentinel node can then be biopsied in the breast clinic. Adapted from a swine melanoma model, it was initially described in 2009 by Sever at al at Maidstone, Kent and Omoto et al in Japan. Sentinel lymph nodes identified with CEUS correlate well with those identified using standard intra-operative tracers. Other academic groups in Europe, Asia and the USA have trialled the procedure indicating that it is a potentially straightforward technique for experienced imaging specialists. The whole procedural time is 15-30 minutes; it is safe and well tolerated by patients and can be performed using ultrasound equipment in widespread clinical use.

B-mode axillary ultrasound, as the current standard of care, usefully recognizes approximately 50% of metastatic lymph nodes and evidence indicates that a subsequent CEUS sentinel node core biopsy can identify a further 50% of metastatic axillary lymph nodes, thus enhancing the overall diagnostic

performance of pre-operative ultrasound. Despite only having a 50% sensitivity, the CEUS sentinel node core biopsy has a high negative predictive value (87%) and any lymph node metastases that are undetected are likely to be low volume and consequently of questionable clinical significance. This was shown in a large (1361 patients) prospective dataset from Maidstone Hospital, where less than 2% of patients with a normal B-mode axillary ultrasound and a benign CEUS sentinel core biopsy had 2 or more axillary LN macrometastases found at the end of surgical treatment. The majority of false negative cases had isolated tumour cells (ITC), micrometastases or a single lymph node macrometastasis with or without additional ITC/ micrometastases . These results were not just confined to patients with favourable tumour characteristics and also included those with large (>50mm) and multifocal cancers.

Finding sentinel lymph node metastases early on in the patient pathway can also help clinical decision making such as changing the first treatment from surgery to chemotherapy. For those patients having a mastectomy, finding a metastatic sentinel lymph node could mean that they require radiotherapy after a mastectomy and this may affect their choices of breast reconstruction.

With this study, we are going to run a training course for imaging specialists to learn how to use intradermal microbubbles and CEUS to find and biopsy sentinel lymph nodes. A video tutorial will also be provided. Each participating imaging specialist will then perform 25 procedures independently with mentorship provided by imaging specialists experienced in performing the procedure. We will also collect information about how good the procedure is at detecting sentinel lymph node metastases.

All experienced breast imaging specialists from participating hospitals can be involved in this study. Each hospital will put forward 2 imaging specialists for this study.

The training course will take place at Maidstone Hospital in Kent and The University of Warwick medical school clinical trials unit will collect and analyse the information about how the procedure performs as a test to find sentinel lymph node metastases. Patients involved in the study will be ask to fill out a satisfaction questionnaire after the procedure and after armpit surgery.

We are planning to run the study over 2 years and hope to involve 10 imaging specialists.

What would taking part involve?

- If you agree to take part, you will need to come to Maidstone Hospital for a training course, which will take place over 1 day. Travel costs will be covered and food and drink will be provided.
- After attending the course, you will be given a video tutorial as well as written information about the procedure.
- You will be assigned a mentor.
- In your own breast unit, you will then perform 25 procedures using

intradermal microbubbles and CEUS independently on patients newly diagnosed with invasive breast cancer and a normal B-mode axillary ultrasound/ benign biopsy of morphologically abnormal lymph nodes. Your mentor will be available to talk on the phone if you have queries or if necessary, travel to your hospital to watch you perform the procedure and guide you if you are having difficulties.

- During the time period of the study, your unit would also prospectively audit the numbers of patients with early breast cancer and an abnormal B-mode ultrasound with a malignant lymph node biopsy.

What are the potential benefits in taking part?

You will learn a new ultrasound procedure that can provide more information about axillary metastases for patients with breast cancer. This procedure also has the potential to replace armpit surgery for large numbers of breast cancer patients.

What are the potential disadvantages and risks of taking part?

You will need to travel to Maidstone in Kent for the training day. The costs of the procedure are covered so your department should not need to find extra funds for the study. However, as using CEUS to biopsy sentinel lymph nodes is not part of your routine practice, your service will need to accommodate the extra 30 minutes/ per patient needed to perform the procedure. In addition after the biopsy, the results will need to be discussed in your multi-disciplinary meeting and the patient will need another clinic appointment with their surgical team to get the results of the sentinel node biopsy. This may put a bit of pressure on your service but the numbers of patients are relatively small at 50 over 2 years (25 for you and 25 for your colleague). The risks are the same as those of any other minimally invasive biopsy procedure such as needle stick injury.

How is your personal information protected?

All information collected about you for this study will be subject to the General Data Protection Regulation and Data Protection Act 2018 and will be kept strictly confidential. Maidstone and Tunbridge Wells NHS Trust are the sponsor for the study, based in the United Kingdom and will act as data controller for the study, this means that they are responsible for looking after your data and using it properly.

The only information we need to collect about you are your initials and hospital site. The trial office will maintain a trial database and this will meet industy-standard security criteria and will only be accessible to authorized personnel. You may also wish to access your own personal performance information and you can do this at any time.

Personal Information about you will be kept for at least 5 years after the study has finished, to allow the results of the study to be verified if needed. The results and the raw information from your assigned study number will then exist in the

database without the link to your personal information. In this way, the results of the study can be shared with other researchers so they can benefit from any new findings. This is an important way to keep medical research moving forward. Any such request is carefully considered by the study researchers and will only be granted if the necessary procedures and approvals are in place.

At any point, you can request to withdraw from the study, without giving a reason and this will not effect your treatment or your care.

Who has organized and funded this study?

The co-investigators are multi-disciplinary and represent breast imaging specialists, breast surgeons, breast oncologists and breast pathologists from across the UK as well as statisticians from Warwick Clinical Trials Unit and a patient representative. The sponsor of the study is Maidstone and Tunbridge Wells NHS Trust. Breast Cancer Now has funded the study.

Further information and contact details

Please contact the Karina Cox at Maidstone and Tunbridge Wells NHS Trust if you want more information about this study on 01622 22 4111 (karina.cox@nhs.net).

How will I know about the results of the study?

The results of the study will be presented at national and international conferences and be published in a Medical Journal as well as on the Breast Cancer Now website.