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Original article

# Multidetector CT improving surgical outcomes in breast cancer (MISO-BC): A randomised controlled trial

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ABSTRACT

*Background:* Early diagnosis of malignant axillary nodes in breast cancer guides the extent of axillary surgery: patients with known axillary malignancy receive a more extensive single operation at the same time as surgery to their breast. A multicentre randomised controlled trial assessed whether a Computed Tomography (CT) scan of the axilla could more accurately diagnose malignant axillary lymph node involvement in patients with newly diagnosed breast cancer when compared to usual care.

*Methods:* Patients with newly diagnosed breast cancer (identified via screening and symptomatic pathways) at two NHS Trusts in the North East of England were recruited and randomised in equal numbers. Both groups received routine diagnostic and surgical care. In addition, one group received a CT scan of their axilla on the same side as the breast cancer. The primary endpoint was the need to undergo a second axillary surgical procedure.

*Findings:* The trial recruited 297 patients of whom 291 contributed to findings. The proportion of patients undergoing a second operation was similar (CT vs UC: 19.4% vs. 19.7%; CT-UC: −0.3%, 95% CI: = −9.5% to 8.9%, $\chi^2$ [1]: p = 1.00). Patients in the two groups were similar before treatment, had similar types and grade of cancer, experienced similar patterns of post-operative complications and reported similar experiences of care.

*Interpretation:* CT scan-guided care did not result in a change in the number of patients requiring a second operation; similar numbers of patients needed further axillary surgery in both groups. New diagnostic imaging technologies regularly enter NHS centres. It is important these are evaluated rigorously before becoming routine care.



## 1. Introduction

Breast cancer is the most common cancer in the UK despite the fact that it is rare in men. In 2013, there were 44,831 new cases of breast cancer diagnosed in the UK; comprising 44,540 (>99%) cases in women and 291 (<1%) cases in men [1]. In England, data from 2004 to 2006 indicated that 83% of patients presenting with breast cancer had breast and axillary surgery or a major resection [2].

Accurate pre-operative axillary staging is essential in planning the management of patients with newly diagnosed breast cancer to inform the most appropriate axillary operation.

Techniques of assessing axillary nodal status vary considerably between centres in the UK. Generally, ultrasound is used with or without fine needle aspiration cytology and core biopsy as a first line investigation. Whilst ultrasound-based techniques of staging are the most commonly used, other investigations to visualise and stage axillary nodal tissue in patients presenting with breast cancer are rarely used but include magnetic resonance imaging (MRI) [3] and Positron emission tomography (PET) or PET integrated with computed tomography (PET-CT) [4].

In the UK, when malignancy has spread to the axillary lymph nodes and is detected prior to surgery, axillary lymph node dissection (ALND) is normally indicated. Though more recently, there has been a shift in surgical opinion towards the potential for

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axillary conservation. Without definitive clinical or radiological evidence of malignancy in the axillary nodes, sentinel lymph node biopsy (SLNB) is usually undertaken (often with blue dye injection as an adjunct) to stage the axillary disease at the time of breast surgery for the breast malignancy. SLNB involves injecting the radiopharmaceutical technetium 99m-labeled albumin colloid via periareolar injection into the breast preoperatively. The most radioactive node in the axilla (the sentinel node) is identified intraoperatively by the surgeon, and is removed and sent for histopathological assessment. ALND involves the removal of all visible nodal tissue in the axilla. The operation carries considerable risk of long-term morbidity; lymphoedema is the most debilitating of these.

Currently 25% of patients undergoing SLNB have histologically confirmed lymph node involvement and subsequently require ALND [5]; further surgery increases the risk of complications and morbidity.

The accuracy of pre-operative staging with ultrasound is dependent on a number of factors including both the operator and test performance. A small retrospective case series comparing ultrasound with core needle biopsy, found a negative predictive value of 89% [6].Another small retrospective study of ultrasound guided final needle aspiration (FNA), found a positive predictive value of 100% and a negative predictive value of 79% [7]. A prospective case series evaluated 102 patients with axillary ultrasound and subsequent core biopsy; the negative predictive value was found to be 73% [8].

A meta-analysis of data from 21 studies (4313 subjects) reported the median ultrasound sensitivity of 61.4%, with a specificity of 82% in detection of axillary nodal metastases. A subset of 1733 subjects from the meta-analysis was selected for ultrasound normal biopsy based on the ultrasound pictures. The median ultrasound sensitivity for the nodal biopsy was 79.4% and the median ultrasound node specificity was 100%. This meta-analysis indicates that the sensitivity of ultrasound alone as a staging technique is modest and cannot be reliably used to reassure patients regarding the absence of axillary nodal metastases. There is clear clinical difficulty in a test resulting in a false negative result of axillary node involvement, in which nodal disease is present but not detectable by conventional ultrasound techniques preoperatively [9].

Multidetector CT is an imaging technique that is rapidly performed and well tolerated by patients, but is not widely used within this area of clinical practice. Several studies have retrospectively evaluated CT assessment of axillary lymph nodes in patients with breast cancer [10,11]. One prospective trial recruited 107 Japanese women with breast cancer to have axillary CT scans. Based on size criteria, CT demonstrated a sensitivity of 76% and a positive predictive value of 95% in predicting lymph nodemetastasis [11].

Robust evidence is needed to understand the potential value of CT scans to improve pre-operative axillary staging in patients with newly diagnosed breast cancer. Consequently a trial was designed to evaluate the utility of multidetector computed tomography in this patient group.

## 2. Methods

### 2.1. Study design

A multicentre randomised controlled trial using a PROBE (prospective randomised open, blinded end-point) design compared usual diagnostic care with CT-enhanced diagnostic care in patients presenting with primary breast cancer and in whom axillary surgery was planned.

The trial was conducted at two large teaching hospitals in the North East of England, United Kingdom. Ethical approval for the protocol and all supporting documents including the participant information sheet and consent form was obtained prior to the study starting from Newcastle and North Tyneside 1 Research Ethics Committee, an independent ethics committee of the NHS National Research Ethics Service.

### 2.2. Patients

The trial recruited adults, female and male, with histopathologically confirmed, newly diagnosed breast cancer, in whom axillary surgery was planned. Patients had undergone ultrasound or mammography prior to entry into the trial, and were able to provide written informed consent.

Patients were excluded if they were medically unstable, had a known allergy to iodinated contrast media, had severe allergic diasthesis, or required renal dialysis. Patients who had already received radiotherapy or surgery to the ipsilateral axilla, were receiving ongoing chemotherapy for a malignancy other than their current breast cancer, required neoadjuvant chemotherapy for their current cancer, were pregnant, or had previously participated in the trial, were also excluded.

All patients provided verbal consent over the phone at trial entry, and written consent at their next hospital visit. The process of consent to the trial was approved by the ethics committee.

### 2.3. Randomisation and masking

Patients were randomised in a ratio of 1:1 to receive usual diagnostic care or usual diagnostic care plus a CT of their axilla. Randomisation was stratified by operating surgeon and according to three age groups; patients aged 46 or below, patients aged 47–69, and patients aged 70 or older at the time of presentation. Patients were randomised using a block size of 4; the clinical team were not informed of the block size used.

Randomisation tables were generated by a statistician at Durham Clinical Trials Unit; password-protected, web-based access enabled clinical teams at the participating centres to randomise patients. On the basis of the stratification variables entered, the next available randomisation allocation was assigned and sent by email to the clinical team, as well as being displayed on the system. The randomisation tables were held centrally by Durham Clinical Trials Unit; users accessing the system were only shown the allocation for the patient being randomised, ensuring concealment of allocation. The nature of the trial intervention meant that clinical research teams and patients knew the allocation. The trial statistician was only given access to assigned groups once the database was locked for final analysis.

### 2.4. Trial procedures

Patients in both arms of the trial had already undergone a routine axillary ultrasound examination with or without core biopsy at the time of their initial assessments and prior to trial entry. Following consent, patients in the usual care arm progressed directly to axillary and breast surgery as planned. Patients randomised to receive an axillary CT scan received this prior to their first planned operation for their breast cancer. Surgery was not delayed by taking part in the trial.

All axillary imaging was performed on a helical multidetector CT scanner of at least 64 slice imaging capacity from one of the following manufacturers: Siemens, General Electric (GE), Phillips, or Toshiba.

Patients receiving an axillary CT scan had an intravenous cannula placed in their contralateral arm or hand from the side of the