

Multidetector CT Improving Surgical Outcomes in Breast Cancer (MISO-BC): A Randomised Controlled Trial

Julie Cox¹
Helen Hancock²
Rebecca Maier²
Jonathan Spratt¹
Chooi May Lee³
Amir Bhatti⁴
James Mason⁵

Corresponding Author: Julie Cox, Department of Radiology, City Hospitals Sunderland Foundation Trust, Kayll Rd, Sunderland, SR4 7PT, UK

Email: julie.cox@chsft.nhs.uk

¹ Department of Radiology, City Hospitals Sunderland Foundation Trust, Kayll Rd, Sunderland, SR4 7PT, UK

² Durham University, Queen's Campus, University Boulevard, Thornaby Stockton-on-Tees, TS17 6BH, UK

³ Perth Radiological Clinic, Perth, Australia

⁴ Department of Surgery, University Hospital North Durham, North Rd, Durham DH1 5TW, UK

⁵ Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK

before becoming routine care. **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%, χ^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

Funding:

The National Institute for Health Research's Research for Patient Benefit Programme

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 2004-2006 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 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 ALND⁵; 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 fine 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 cancer¹⁰⁻¹¹. 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 nodemetastasis¹¹

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.

Methods

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.

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.

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.

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 known breast cancer. The patient's arms were positioned above their head. Non-ionic contrast medium (Niopam 300 or equivalent) was injected at a volume of 100 ml, at a rate of 3 ml per second. Imaging was performed after a delay of 40 seconds from the start of the injection. The radiographer set the scan range from the top of the chest to the bottom of the scapula using the scanning parameters as detailed in table 1.

The field of view (FOV) was collimated from the skin surface to the lateral border of the vertebrae (on the affected side), to ensure imaging was confined to the axilla; it was not the purpose of the scan or the trial to detect occult metastatic disease.

Axial images were reconstructed at 3 mm slice widths on soft tissue and lung algorithms in the coronal and sagittal planes. All three sets of images (axial, coronal,

and sagittal) were reported centrally at the lead centre by one of two consultant radiologists who were also part of the research team. Scans were reviewed and reported independently of other usual care imaging findings. Images were reviewed for: number of axillary lymph nodes present, size of the axillary lymph nodes, morphology (shape) of the nodes in terms of cortical irregularity and cortical thickness and enhanced pattern. The following criteria were included where relevant on the CT reports: multiple nodes greater than 5mm; irregular, non-ovoid nodes (<2:1 long to short axis in diameter); loss of normal fatty hilum; cortical thickness greater than 3mm; enhancement of more than 20 Hounsfield units compared to a node with normal appearance.

Axillary lymph nodes with four or more criteria were considered highly suspicious. Axillary lymph nodes with 2-3 criteria were considered equivocal. Axillary lymph nodes with one or fewer criteria were considered benign.

The report of the findings of the CT scan was used to inform the multi-disciplinary team (MDT) decision-making process. Together with the results of axillary ultrasound, the CT scan results were discussed at the Breast MDT and the appropriate axillary surgery (either SLNB or ALND) determined. Where time did not allow, the results were discussed directly with the operating surgeon and changes to the planned axillary surgery were made as appropriate.

Following surgery, the CT scan results were correlated with histopathological results obtained during axillary surgery (the reference standard) to determine the sensitivity and specificity of the CT examination. Histopathological determination was

conducted by a pathologist blinded to CT scan findings. Thus the performance of ultrasound (+/- core biopsy) and CT alone and in combination were estimated.

Patients were followed for up to four weeks following their final episode of axillary surgery. Following histopathological confirmation that no further axillary surgery was required, patients were asked to complete a patient experience questionnaire, marking their completion in the study. Adverse events were recorded for both groups to the point of questionnaire completion.

Outcomes

The primary outcome was the change in the rate of re-operation on the axilla, comparing usual diagnostic care and usual diagnostic care plus CT of the axilla. Re-operation occurred when patients who had been determined suitable for sentinel lymph node biopsy as their first axillary operation, had histopathologically confirmed disease in the excised axillary lymph node and thus required further surgery in the form of axillary lymph node dissection.

Secondary outcomes were:

- patient satisfaction determined using a patient satisfaction questionnaire completed over the phone by patients at the end of the study;
- the test performance of routine perioperative imaging with and without multi-detector CT in correctly selecting patients for surgery against histopathological reference standard findings;
- the sensitivity, specificity, and positive and negative predictive values of ultrasound of the axilla, ultrasound with needle sampling and multidetector CT;
- economic analysis; and

- rates of common post-surgical complications.

Statistical Analysis

Assuming alpha of 5% and power of 90%, a sample of 143 patients per group (286 in total) was required to detect an absolute difference in reoperation rates of 15% (25% in the control group and 10% in the intervention group). The study recruited 297 patients between January 2011 and February 2014.

The need for re-operation of the axilla was estimated as the difference in proportions between the two groups using Fisher's exact test. Primary inference was based on the primary endpoint analysis of the intention-to-treat (ITT) population, with statistical significance assessed at the 5% level (2-sided). Logistic regression adjusted for stratifying factors (age and surgeon) provided secondary (supportive) analysis of the primary endpoint. Logistic regression findings were presented exponentiated as odds ratios (OR).

Secondary measures involving categorical variables were estimated using Fisher's exact test, with approximate (Miettinen) confidence intervals for reported proportions; continuous measures were evaluated using Student's t-test, or non-parametric tests when required. Correlations between tests were estimated using the Spearman's rank test.

Adverse events were summarised and tabulated. Rates of adverse events were compared using negative binomial regression, with findings presented exponentiated as the incident rate ratio (IRR).

A cost analysis of the hospital care provided to intervention and control groups was conducted, including procedural data, from an NHS perspective and using bootstrap methods. Costs of procedures were obtained from national data. A cost-consequences analysis was planned, setting incremental costs against reoperation rates, complications and levels of patient satisfaction.

The trial was overseen by an independent data monitoring committee (IDMC) who met every four months for the duration of the trial. The IDMC adhered to a trial specific DAMOCLES charter.

The trial was registered with the International Standard Randomised Controlled Trial Number database (ISRCTN03659464).

Role of funding source

This paper presents the findings of independent research commissioned by the National Institute for Health Research under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number PB-PG-0609-18085). The views expressed are those of the authors, and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Results

The study recruited 297 patients from January 2011 to February 2014, receiving care within two NHS Hospital Trusts in the North-East of England. The recruitment rate was 69% of eligible patients approached. After recruitment, 5 patients were withdrawn and 1 died before surgery leaving 291 patients with outcome data and

contributing to analyses (see Figure 1). Patients received CT-enhanced care (CT) or usual care (UC).

At baseline CT and UC groups were similar in demographic, disease and comorbidity measures (Table 2). Baseline characteristics were well balanced across both groups.

At the first axillary operative procedure, the proportion of patients receiving ALND was similar (CT vs UC: 20.8% vs. 13.6%; CT-UC: 7.2%, 95%CI: = -1.5% to 16.0%, χ^2 [1]: p=0.12) (Table 3). The proportion of patients undergoing a second operation (the trial primary endpoint) was similar (CT vs UC: 19.4% vs. 19.7%; CT-UC: -0.3%, 95%CI: = -9.5% to 8.9%, χ^2 [1]: p=1.00). CT-enhanced pre-operative assessment had no statistically significant impact on the use of more invasive ALND as a first procedure and did not reduce the need for second surgery.

Analysis of the primary endpoint within a general linear model (adjusted for stratifying variables within the randomisation) similarly found no difference between groups: adjusted OR: 1.00, 95%CI: 0.56 to 1.82, p=0.99). Other measures of surgery and disease for first and second surgical procedures were similar for both groups (Table 3). There was no significant difference in cost between groups: CT-UC: £98, 95%CI: -£69 to £250, p=0.25, the non-significant increase being mainly accounted for by the cost of the CT scan (£86).

Axillary ultrasound and CT findings were compared in those patients receiving CT. The correlation between the size of the largest node using the two methods was 0.52 (p<0.01) and number of nodes detected was 0.38 (p<0.01). Similarly, levels of abnormality were significantly correlated: 0.524 (p<0.01) although discrepancies could account for the marginally higher initial CT group surgery rate if either test

being abnormal led to choosing more radical surgery (Table 4). It was not possible to compare the test accuracy of CT and ultrasound against the post-surgery histopathology indication for surgery. Although 'false negatives' were known (those in whom histopathology after first surgery identifies the need for a second radical operation), false positives were not known (those in whom histopathology does not confirm the selection of initial radical surgery).

Patients completed a questionnaire following final surgery, which assessed their experience (Table 5). The level of distress from procedures and surgery was similar between groups, and levels of distress from CT were similar to those reported for mammography.

Four adverse events (AEs) were reported related to receiving a CT scan: 1 report each of polyuria (mild), pruritus (moderate), pyrexia (mild) and nausea (mild). No serious AEs were reported related to receiving CT. Reported AEs due to first and second surgery were similar between groups (Table 6). The total number of reported AEs per patient was CT: 3.4 and UC: 3.2; IRR: 1.08, 95%CI: -0.83 to 1.40, $p=0.55$. The total number of reported AEs rated as severe per patient was CT: 0.15 and UC: 0.06; IRR: 2.46, 95%CI: 1.10 to 5.52, $p=0.03$.

Discussion:

Identifying the presence of axillary lymph node metastasis in patients presenting with breast cancer is crucial in the decision-making process for determining the optimum treatment for the patient. Sentinel lymph node biopsy is the definitive method used to exclude axillary metastases, but this is an invasive surgical staging technique. Patients with SLNB results indicating axillary lymph node metastasis generally

undergo axillary lymph node dissection. In our trial, the addition of multidetector CT (with equipment of at least 64 slice capacity) to the patient pathway did not diminish the need for additional surgery, nor improve surgical outcomes or patient experience. It should be noted that a higher percentage of patients in the CT arm of the study did have ALND as a first procedure, 20.8% compared with 13.6% in the usual care group which suggests information from the CT scan about the nodal status is influencing the choice of initial surgery as in all other respects, the two control and study group were matched.

Our study is however unique in that a diagnostic test was evaluated in a randomised fashion with a robust clinical outcome as the primary end point. Although there are numerous retrospective reviews and prospective studies evaluating test accuracy, this is, to the authors' knowledge, the only study to evaluate the clinical utility of multidetector CT in a practise setting with the purpose of informing decisions about its adoption as a diagnostic intervention.

The trial achieved an excellent recruitment rate (69%) of eligible patients who despite going through an extremely difficult life experience in their being diagnosed with cancer, were keen and motivated to take part in this trial. For the trial team, the logistical challenge of organising an additional CT scan, reporting the scan results, incorporating these into the clinical care pathway and MDT discussion where possible was challenging. In the context of this clinical pathway in which time is necessarily limited (the length of time from diagnosis to first operation for each patient was in the order of two weeks), this achievement should not be underestimated.

It is now becoming clear from clinical studies such as the ACOSOG Z0011 research

study that a selected group of SLNB positive patients may be able to avoid ALND.

In a retrospective study of practice in the USA, from information contained on the National Cancer Data Base, Bilimoria reported on 97314 patients; 23% of patients with SLNB macro metastases and 36% of patients with SNB micrometastases did not have ALND, yet for both groups with small volume nodal disease (pN1 and pN1m1) the axillary local recurrence rate and five year survival were the same as the group who had undergone the ALND.¹² A number of other smaller retrospective studies have demonstrated low rates of axillary recurrence (0-2% in 28-82 months follow up) of patients who have had SLNB but have not gone on to have a ALND. The most robust evidence comes from the Z0011 trial, a prospective RCT in which 813 patients with SLNB results indicating axillary lymph node metastasis were randomised to ALND versus no further surgery. Additional positive nodes were found in 27% of patients who had ALND, but at six years follow up there were no significant difference between the ALND and no ALND arms in local, regional or overall loco-regional recurrences, or in disease free survival.¹³ In the UK, the HTA has funded the POSNOC study¹⁴, a multicentre randomised controlled trial, addressing the same topic, although given the prolonged length of follow-up needed to accurately assess local recurrence in particular, it may be seven to eight years before the results of this trial are known.

As there is a trend generally toward more conservation and less radical surgery in the axilla, many would argue the pre-operative staging of the axilla is becoming of greater importance. While ultrasound with needle biopsy technique remains standard practice internationally, it should be remembered that this diagnostic technique has not been studied in the context of a rigorous RCT.

It is likely that clinical questions about surgery involving the axilla will not be restricted by a binary solution of a positive/negative result, but rather will involve an assessment of the overall burden of disease, as it may well be that low volume axillary disease, found at SLNB, is better managed conservatively. Multidetector CT as an imaging tool provides standardised images in multiple planes, and gives an excellent overview of the anatomy of the axilla, the number of nodes present and the proximity of the nodal disease to structures such as the axillary vein. As has been demonstrated in our study, a simple but clear CT protocol can be supplied to experienced radiographers in two separate hospital sites with different CT equipment, and high quality and comparable images consistently achieved. The intra-operator variability associated with ultrasound and variability of ultrasound equipment performance is therefore avoided.

Multidetector CT may have a role in the future in evaluating disease burden prior to axillary conservation and in imaging follow up of the “conserved” axilla. Further research using the latest generation of CT scanning equipment is needed to evaluate the clinical utility of CT in this different context and in the new world order of less radical surgery to the axilla.

Conclusion:

In conclusion, in this trial 20% of patients receiving usual care or usual care plus CT needed a second procedure; this is lower than the historical rate of 25%. The addition of multidetector computed tomography (CT) to the diagnostic assessment of patients with newly diagnosed breast cancer did not support the hypothesis that the reoperation rate of axillary surgery could be reduced to 15%.

New diagnostic imaging technologies are regularly introduced NHS centres. It is important these are rigorously evaluated before becoming routine care. In patients with newly diagnosed breast cancer, the addition of an axillary CT scan was not found to reduce the need for further axillary operations, or to improve surgical outcomes or patient experience

Contributors

JC was the lead investigator, who co-designed and conducted the trial, contributed to the interpretation of findings and to the writing of the report

HH was a trial methodologist, who contributed to the design and to the interpretation of findings and to the writing of the report

RM was the senior trial manager, who contributed to design and the interpretation of findings and to the writing of the report

JS was an investigator, involved in the conduct of the trial, and contributed to the interpretation of findings and to the writing of the report

CML was an investigator, involved in the conduct of the trial, and contributed to the interpretation of findings and to the writing of the report

AB contributed to the study development and to the clinical interpretation of the results.

JM was a Health Economist and Statistician, who co-designed the trial, conducted the analyses, contributed to the interpretation of findings and to the writing of the report

Declaration of interests

The authors have no competing interests

Acknowledgements

The research team would like to thank the research nurses, breast care nurses, radiologists and staff at the two research sites whose help and support was essential to delivery of the trial. The research team would also like to thank the staff at Durham Clinical Trials Unit.

The research team would also like to thank Ms Andrea Kay, Project Manager and Mrs Enid Wright, Research Sister, for their superb efforts in managing the trial and in patient recruitment.

References

-
- ¹ <http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcM%3A77-394268>, accessed 12/1/16
 - ² Major Surgical resections England, 2004-2006.(2011) National Cancer Intelligence Unit
 - ³ Mortellaro VE, Marshall J, et al Magnetic resonance imaging for axillary staging in patients with breast cancer. *J Magn Reson Imaging*. 2009 Aug;30(2):309-12.
 - ⁴ Cooper KL, Harnan S, et al. Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: A systematic review and meta-analysis. *Eur J Surg Oncol*. 2011 Mar;37(3):187-98.
 - ⁵ Diepstraten S ,Sever AR, et al Value of Preoperative Ultrasound-Guided Axillary Lymph Node Biopsy for Preventing Completion Axillary Lymph Node Dissection in Breast Cancer: A Systematic Review and Meta-Analysis. *Annals of Surgical Oncology* 2014, 21(1) :51-59
 - ⁶ Abe H, Schmidt RA, et al. Axillary lymph nodes suspicious for breast cancer metastasis:sampling with US Guided 14 gauge core needle core biopsy- clinical experience in 100 patients. *Radiology* 2009; 250: 41-49
 - ⁷ Altomare V, Guerrero G, et al. Axillary lymph node echo-guided fine-needle aspiration cytology enables breast cancer patients to avoid a sentinel lymph node biopsy. Preliminary experience and a review of the literature. *Surg Today* 2007; 37: 735-9. Epub 2007 Aug 27.
 - ⁸ Nori J, Bazzocchi M, et al. Role of axillary lymph node ultrasound and large core biopsy in the preoperative assessment of patients selected for sentinel node biopsy. *Radiol Med*. 2005; 109: 330-44.

⁹ Houssami N, Ciatto S, Turner RM, et al Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. *Ann Surg.* 2011 Aug;254(2):243-51

¹⁰ Yuen S, Sawai K, Ushijima Y, Okuyama T, Yamada K, Nishimura T. Evaluation of axillary status in Breast Cancer. CT based determination of sentinel lymph node size. *Acta Radiologica* 2002; 43:579-586.

¹¹ Yuen S, Kamada K, Gotto M, Sawai K, Nishimura T. CT- based Evaluation of Axillary Sentinel Lymph Node Status in Breast Cancer: Value of Added Contrast-Enhanced Study. *Acta Radiologica* 2004; 45:730-737.

¹² Bilimoria KY, Bentrem DJ, Hansen NM et al. Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. *J Clin Oncol.* 2009 Jun 20;27(18):2946-53

¹³ Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011;305(6):569-575

¹⁴ <https://clinicaltrials.gov/ct2/show/NCT02401685>, accessed 12/1/16