National MARGINS Audit

PROTOCOL

FINAL VERSION 16-11-15

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Table of Contents

Contact details 2
Summary of protocol 3
Introduction 5
Background 5
Rationale for audit 8
Study question 9
Study design 9
Objectives 10
Methods 10
Expected recruitment 11
Eligibility criteria 12
Outcome measures 12
Dissemination 12
Authorship 12
Disclaimer 13
References 13
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Summary protocol

<table>
<thead>
<tr>
<th><strong>Sponsor</strong></th>
<th>St George’s University Hospitals NHS Foundation Trust</th>
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| **Indication** | Service evaluation and policy development |
| **Design** | Multicenter prospective observational audit |
| **Primary Outcome Measures** | Re-excision rates |
| **Secondary Measures** | Margin widths  
Patient demographics  
Presenting symptoms  
Tumour characteristics  
Preoperative radiological measurement of tumour size  
Localisation technique (none/US skin mark/wire guided)  
Intraoperative assessment of tumour margins  
Histological measurement of tumour size  
Wound complications |
<table>
<thead>
<tr>
<th>Study Period</th>
<th>4 months</th>
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</thead>
<tbody>
<tr>
<td><strong>Phase 1: pilot</strong></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; December to 30&lt;sup&gt;th&lt;/sup&gt; December 2015</td>
</tr>
<tr>
<td><strong>Phase 2: National data collection</strong></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; February 2016 to 31&lt;sup&gt;st&lt;/sup&gt; March 2016</td>
</tr>
<tr>
<td><strong>Period of consultation with participating collaboratives</strong></td>
<td>8&lt;sup&gt;th&lt;/sup&gt; June to 6&lt;sup&gt;th&lt;/sup&gt; July 2015</td>
</tr>
<tr>
<td><strong>Deadline for obtaining approval from audit department</strong></td>
<td>25&lt;sup&gt;th&lt;/sup&gt; January 2016</td>
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<tr>
<td><strong>Consultant registration</strong></td>
<td>25&lt;sup&gt;th&lt;/sup&gt; January 2016</td>
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<td><strong>Consultant Questionnaire</strong></td>
<td>25&lt;sup&gt;rd&lt;/sup&gt; January 2016</td>
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<tr>
<td><strong>Submission of Phase 1 data</strong></td>
<td>18&lt;sup&gt;th&lt;/sup&gt; January 2016</td>
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<tr>
<td><strong>Submission of Phase 2 data</strong></td>
<td>29&lt;sup&gt;th&lt;/sup&gt; April 2016</td>
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<tr>
<td><strong>Completion of data analysis</strong></td>
<td>31&lt;sup&gt;st&lt;/sup&gt; May 2016</td>
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<tr>
<td><strong>Results available</strong></td>
<td>20&lt;sup&gt;th&lt;/sup&gt; June 2016</td>
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<tr>
<td><strong>Estimated Manuscript submission</strong></td>
<td>July 2016</td>
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Introduction

The National Margins Audit Committee would like to invite breast surgeons across the UK to collaborate on the National Margins Audit project. This document outlines details of the protocol to be adopted in order to execute the audit.

The National Margins Audit is designed to be a multicentre prospective audit of variation in clinical practice and its influence on re-excision rates and immediate and short term patient outcomes as defined subsequently in this document. All patient data will be anonymized for the purposes of analysis and presentation or publication.

Background

Breast conservation therapy (BCT) has become standard of care for most early stage breast cancers. BCT combines local excision of the tumour followed by adjuvant radiotherapy to the remaining breast tissue. The delivery of radiotherapy is an essential component of BCT in the management of invasive breast cancer.

A review of 6 trials comparing patients managed by local excision alone or surgery plus radiotherapy for breast cancer found that the addition of postoperative radiotherapy reduced the local recurrence risk by over 60% although no survival benefit was seen following radiotherapy in any of the trials (Liljegren, 2002). Furthermore, robust evidence from long term follow-up studies has demonstrated that breast conservation therapy has equivalent survival outcome compared to mastectomy (Morris et al., 1997; Veronesi et al., 2002; Blichert-Toft et al., 2008).

There are a number of advantages that breast conservation has over mastectomy. The preservation of the breast and usually of the nipple areolar complex is important to most patients’ self-image and ability to cope with their diagnosis and treatment. Additional benefits include a shorter operative and anaesthetic time, less post-operative discomfort and reduced likelihood of post-operative complications (such as anaemia, haematoma, seroma, infection and altered sensation). The burden of reconstructive surgery and possible
long term sequelae (donor site morbidity, additional scars, implant related issues etc.) are also avoided. Importantly, a reduction in hospital length of stay and recovery (with earlier return to work) has important economic and financial implications for the NHS Trust and the patient.

Numerous studies have demonstrated local recurrence rates between 3.5% and 7.5% at 5 years following BCT (Leong et al., 2004; van den Broek et al., 2007; Mechera et al., 2009). To date, 6 well-known randomized controlled trials with long-term follow-up have demonstrated overall equivalence between breast conservation therapy and mastectomy for early-stage invasive breast cancer (van Dongen et al., 2000; Fisher et al., 2002; Veronesi et al., 2002; Arriagada et al., 2003; Poggi et al., 2003). Overall survival ranged from 41% to 66% at up to 20 years of follow-up with no significant difference between breast conservation and mastectomy. In 3 of these studies, local recurrence was found to be higher following breast conservation (van Dongen et al., 2000; Veronesi et al., 2002; Poggi et al., 2003). It would appear therefore that while mastectomy may confer some benefit in terms of local control, this does not affect overall survival and likely reflects improved adjuvant treatments and post-operative surveillance regimens.

Despite not affecting overall survival, the development of a local recurrence represents a significant event for the patient. Treatment for a local recurrence following full BCT usually necessitates completion mastectomy as no further radiotherapy can be delivered to a previously irradiated breast. In addition, the patient may be faced with chemotherapy and/or recommencement or extension of their endocrine treatment. In additional to the emotional burden of disease relapse, all these treatments have associated potential morbidities. The development of prognostic indices to identify patients at higher chance of local recurrence is therefore important. Potentially, those at very high risk of local relapse may be counselled to undergo mastectomy as part of their primary treatment or may be offered increased or extended surveillance.

The Nottingham Prognostic Index is used to give a prediction of 5 year survival rates (Fredriksson et al., 2003). Currently used clinical tools such as Adjuvant online and Predict incorporate patient and tumour related factors including age, tumour size, tumour grade,
nodal burden and hormone receptor status to calculate a patient’s mortality risk and is used to identify those who should benefit from adjuvant chemotherapy. Additional information from molecular profiling (e.g. Ki-67 and Oncotype DX) can be used to guide chemotherapy delivery in patients identified to have borderline benefit based on traditional methods of risk assessment. This is of particular importance because chemotherapy is associated with significant comorbidity and a small risk of mortality. However, both Adjuvant online and Predict are based on mortality data and not used to predict local recurrence risk following breast conservation therapy.

In the context of pre-invasive disease (DCIS), adjuvant treatment after surgery remains controversial. To this end, the Van Nuys Prognostic index (VNPI) has been designed to identify patients who have a moderate to high risk for local recurrence and should benefit from adjuvant radiotherapy (Silverstein et al., 1996; Silverstein, 2003). The updated VNPI is calculated by the margin width, size of DCIS, grade (including the presence or not of comedo necrosis) and age (Silverstein, 2003). In practical terms, a re-excision of margins may potentially result in a significant alteration in the VNPI and alter the indication for radiotherapy. Those who remain at high risk of recurrence may be offered mastectomy because up to 50% of DCIS recurrences take the form of invasive disease. The VNPI is now widely used in the clinical setting and is usually recorded during multidisciplinary team discussions.

Numerous studies have examined the factors associated with an increased risk of local recurrence in invasive disease. These include young age, large tumour size, ER negativity, excision margin status, higher grade, tumour multi-centricity, node positivity, the presence of DCIS, an extensive intraductal component (when 25% or more of the carcinoma cells are growing in the intraductal compartment) and LCIS (Yaghan et al., 1998; Fredriksson et al., 2003; Leong et al., 2004; Mechera et al., 2009; Miles et al., 2012).

A recent retrospective audit of 1400 patients undergoing breast conservation at a single institution in the UK found that at multivariate analysis only 2 variables (margin status and ER status) remained significantly associated with local recurrence (Tang and Gui, 2015). Regarding margin status, as expected, patients with involved margins have the highest risk of
local recurrence. The Kaplan Meier analysis shows that this difference is most marked in the first 100 months with very few events after this time. There was also an increased risk of local recurrence in patients who underwent re-excision of margins. While pathological confirmation of margin clearance can be demonstrated in negative margin shaves, this finding questions the accuracy of these shaves when taken at a second operation.

Of particular interest, this study found no difference in local recurrence between clear margins and close margins (<1 mm) margins. These findings are in line with the recent meta-analysis of 33 studies including 28,162 patients. This study found that positive margins doubled the risk of local recurrence compared to negative margins. However, as long as there was no ink on the tumour, wider margins did not significantly alter the local recurrence rate. Importantly, this finding was also true in unfavourable cases such as in younger patients, those with more aggressive tumour biology, lobular cancers or those with an extensive intraductal component.

Based on these findings, The Society of Surgical Oncology and American Society for Radiation Oncology updated their consensus guideline on margins for breast-conserving surgery with whole breast irradiation in February 2014 (Moran et al., 2014). This guideline recommends the use of no ink on tumour as the standard for adequate margin in invasive breast cancer.

Rationale for audit

The recommended margin width following breast conservation therapy in the UK is not clearly defined and considerable variation in accepted margin diameter is seen in units across the country. The subsequent impact on margin re-excision rates nationally has not been previously studied.

In the NICE guidelines for early and locally advanced breast cancer (NICE, 2009), the margin clearance for DCIS is defined at 2mm but a recommendation for the minimum margin width for invasive disease is not made. The London Cancer Alliance Breast Cancer guidelines from October 2013 state that radial margins must comply with the local MDT standard. These
guidelines also state that there are no data to support a specific margin of excision but it should be at least greater or equal to 1mm (LCA, 2013).

In the light of the recent metanalysis on margins and the adoption of “clear at the inked margin” as the standard by the Society of Surgical Oncology and American Society for Radiation Oncology in 2014, even local guidelines including that of the LCA (equal or greater than 1mm) can be considered out of date.

Excessively wide margins may have a detrimental impact on patient outcome. There may be a cosmetic penalty which may be further impacted by radiotherapy. Further procedures such at lipomodelling may be required to address this at additional cost to the NHS. Patients undergoing margin re-excision may suffer worsening cosmesis (when previously considered acceptable) and are placed at an increased risk wound infection, chronic pain, seroma, poor scarring and anaesthetic complications. The process of margin re-excision raises patient anxiety, and places additional burden on already busy theatre lists and may delay the onset of adjuvant treatment. Additional costs are associated with a second (or third) anaesthetic, a hospital bed and further histological analysis.

Study question

“Is there variability in the margin re-excision rate across breast units nationally and how is this related to accepted margin widths and other patient and tumour related factors?”

Study design

Multicentre prospective observational audit.
Objectives

To define:

Management trends across centres
Regional variations
Short term outcomes:
  - Re-excision rates
  - Wound complications
Parameters for future trials/interventional/observational studies

Methods

Any UK centre providing breast cancer services is eligible. A trainee lead will be identified at each unit through the trainee collaboratives. There have been numerous examples of successful trainee led studies in the UK. These include the implant Based Reconstruction Audit (iBRA –SPARCS) and the National Complicated Acute Diverticulitis Audit (CADS – YRSC). With high volume cases such as wide local excisions for breast cancer, a prospective audit of patients in a short audit period of 2 months across many units across the country should provide sufficient data. This will also allow the trainee leads to complete the data collection phase of the audit before they rotate to their next post. Trainees should approach and nominate a consultant surgeon as principal investigator (PI) who would support the smooth conduct of the study in that centre.

Each centre must provide at least 20 patients within the 2 month period to be eligible for inclusion in the analysis stage. Prior to the commencement of the audit, an anonymized questionnaire would be sent out to all trainee leads to complete with their nominated consultant evaluating the unit policies with regards to the management of margins in breast cancer. This is only for purposes of comparing approaches with outcomes and individual surgeons or units will not be identifiable in the analysis of results.
Study periods

Phase 1: Pilot study

Data collection in 3 units will commence on 1\textsuperscript{st} December 2015 from 0800hr and cease on 30\textsuperscript{th} December 2015 at 2000hr

Phase 2: National data collection

Data collection nationally will commence on 1\textsuperscript{st} February 2016 at 0800hr and cease on 31\textsuperscript{st} March 2016 at 2000hr.

Mode of data collection

All data must be entered in the secure online REDCap database using the provided access details only. Any hard copies of data must either be destroyed or kept safely until the data has been uploaded on the database.

Each centre will be allocated a unique Centre ID. Data entered into REDCap is stripped of all patient identifiers. The trainee lead should therefore create a study ID for each patient using the centre ID as a pre-fix. A secure Excel file containing study IDs and corresponding patient hospital number should be kept by the trainee lead so that they can be referenced in the future if necessary.

Expected recruitment

In 2010, the Office for National Statistics recorded 41,259 new cases of breast cancer in England (Statistics, 2012). Of new breast cancers, approximately 57% undergo breast conservation therapy (American Cancer Society, 2013)

An estimated 450 patients therefore undergo wide local excision in England every week. It is anticipated that most centers will perform at least 3 wide local excisions a week, with most centers perform greater numbers. Thus over a 2 month period, it should not be difficult for most centers to achieve their minimum data set of 20 patients.
Eligibility criteria

All women with DCIS or invasive breast cancer treated by wide local excision as their first mode of treatment.

Outcome measures

Primary outcome

Re-excision rate

The following secondary outcomes will also be evaluated

- Margin widths
- Patient demographics
- Mode of presentation (symptomatic, screen detected)
- Tumour characteristics
- Preoperative radiological measurement of tumour size
- Localisation technique (none/US skin mark/wire guided)
- Intraoperative assessment of tumour margins
- Histological measurement of tumour size
- Wound complications

Dissemination

Participants may present their local data at their department clinical governance meeting. National data shall be presented at a national conference and will be submitted for publication in a peer-reviewed journal.
Authorship

We will aim to publish using the desired authorship model of the LSRG which is where the paper is authored under “London Surgical Research Group” and then all investigators are listed in the PubMed citable author section in order of contribution. Publications using only local or part of the national data set must include members of the National Margins Audit Core group as named authors.

For more information on this authorship model please see:
http://www.lsrg.co.uk/about-us/how-it-works.

Disclaimer

The National Margins Audit core committee reserves the right to review and amend this protocol within reason during the course of the audit to enable delivery of the project to the highest standards.

References


