Sentinel Node Biopsy using Magnetic Nanoparticles: A prospective multicentre phase II non-randomised clinical trial to compare sentinel node biopsy using magnetic nanoparticles vs. standard technique

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON40081

Source
ToetsingOnline

Brief title
SentiMag Multicentre Trial

Condition

- Breast neoplasms malignant and unspecified (incl nipple)
- Breast therapeutic procedures

Synonym
1) Sentinel Lymph Node metastases in breast cancer patient 2) Cancer in the Sentinel Lymph Node(s)

Research involving
Human

Sponsors and support

Primary sponsor: King's College London
Source(s) of monetary or material Support: Unrestricted educational grant from Endomagnetics Ltd.

Intervention

Keyword: MRI, SentiMag, Sentinel Lymph Node biopsy, Sienna+

Outcome measures

Primary outcome

Primary end-point: The proportion of sentinel nodes detected (detection rate) with either the standard (patent blue dye and radioisotope; or radioisotope alone) or the new technique (magnetic tracer and hand-held magnetometer).

Secondary outcome

Secondary outcome measures: Morbidity from SLNB including lymphoedema, numbness, seroma, cutaneous staining, shoulder stiffness, chronic pain and locoregional recurrence.

An initial cost-effectiveness evaluation of the new technique will also be performed.

Outcome measures MRI subprotocol: evaluate the accuracy of MRI for the localisation of the SLN and the detection of metastasis (macro and micrometastases).

Study description

Background summary

The SentiMag Multicentre Trial is a continuation of two earlier conducted studies (see section 1.3 and 1.4 in protocol). The initial clinical pilot study was conducted by the Chief Investigator, Mr Michael Douek, at University College Hospital. Ten patients with newly diagnosed breast cancer scheduled for sentinel node biopsy were recruited prior to surgery. These patients received a radioisotope injection and underwent lymphoscintigraphy a day prior to surgery. On the morning of surgery, they received a subcutaneous injection of a SPIO tracer (Endorem, Guerbet, Paris) in the MRI Department. Dynamic axillary MRI before and after injection of the SPIO identified lymphatic tracts and sentinel nodes in 5/6 patients (1 scan failed for technical reasons). Under general anaesthetic, patients routinely received an intradermal injection of patent blue dye (Guerbet, Paris). The sentinel node(s) were localised using both a gamma probe and magnetometer prototype I. Skin localisation with magnetometer prototype I and the gamma probe, were identical. A total of 19 sentinel nodes were resected from 9 patients. Intra-operative localisation using the combined technique was successful in detecting 19/19 (100%) nodes and using magnetometer prototype I alone in 19/19 (100%). Once found by the surgeon, most sentinel nodes were easily identified as black from SPIO deposition.

Following the initial pilot study, several challenges were identified, including interference from large metal objects, the shape of the probe and the stability of the magnetic field. These were rectified and a second prototype developed (prototype II). The Chief Investigator relocated to Guy*s Hospital and a further 43 patients were recruited into an extended phase I/II trial. The overall ex-vivo SentiMAG Multicentre SLN detection rate was 86% (37/43 patients) and was higher in patients who received SPIO more than 1 hour prior to surgery (93%, 14/15). Data on the laboratory performance of the CE-marked SentiMag and prototype II, were comparable and was included in the application for CE approval. The first
sentinel node biopsy using the CE-marked SentiMag was performed successfully on the 6th December 2010. Ethics Committee approval to commence a phase II clinical trial at Guy*s Hospital to recruit 130 patients, has already been granted.

Study objective

The principal objective of the study is to determine if the performance of the new technique (magnetic tracer and magnetometer) is equivalent to the performance of the standard technique (patent blue dye and radioisotope; or radioisotope alone).

The primary objective of the axillary MRI is to localize the SLN, the secundary objective of the axillary MRI and the ex-vivo MRI is to determine if MRI can be used as a non-invasive method for identification of breast cancer metastases in lymph nodes.

Study design

The SentiMAG Multicentre Trial is a phase II paired equivalence trial. It will initially involve 6 centres and will be co-ordinated from King*s College London (Guy*s Hospital) by the Chief Investigator. The trial aimed to recruit 176 patients (assuming up to 10% patient drop-out). Centres will be invited to recruit 30 patients and the trial will be closed once the target number of 160 complete patient datasets has been reached.

Patients will receive a radioisotope injection and a subcutaneous, periareolar injection of Sienna+. This may be given between up to thirty minutes before surgery. In centre's that also participate in the MRI subprotocol, patients will undergo a pre-operative axillary MRI scan before and a after injection of Sienna+. At the Medisch Spectrum Twente pre-operative axillary MRI scans will be performed depending on the availibility of the MRI scanning slots.

Intra-operatively, patients will receive an intradermal injection of patent blue (Guerbet, Paris). All sentinel nodes detected intra-operatively using either the gamma probe or SentiMag; or demonstrating blue or black staining will be excised. In the lead centre (and any other sites participating in the MRI subprotocol), ex-vivo MRI scans of the excised nodes will be undertaken using a high-resolution MRI scanner. In Enschede the ex-vivo MRI scans will be undertaken at the University of Twente using the 14.1T MRI scanner. Furthermore, at the University of Twente in Enschede the amount of iron in each excised node will be measured using a quantitative magnetometer.

All lymph nodes will be assessed histologically and the nodal status will be related back to the SLNB detection rate with each technique.

Patients will be followed up post-operatively (7-14 days after surgery) to assess if staining occurs or for any other adverse event. If staining is present, photographs will be taken. Further follow-up is at 3 months and at 1 year. Patients will be followed up for a total of 5 years, in accordance with current local policies.

Following completion, a selection of centres that achieved at least a 92% sentinel node detection (per patient), will be invited to proceed with the phase III randomised controlled trial.

Intervention

The Medisch Spectrum Twente will participate in the MRI subprotocol. As part of the MRI-subprotocol, patients will undergo an MRI scan of the axilla prior to the scheduled operation. The scan will take roughly 60 minutes and involves lying down in a tubular scanner. Once positioned in the scanner, an initial scan will be undertaken. Following the initial scan, an subcutaneous periareolar injection of 2ml Sienna+ is given into the breast and a second scan is performed. The scan may need to be repeated at 2 hours or at 24 hours after the initial scan but further injections will not be required.

The operation will be performed as already planned by the surgeon. In addition to the normal blue dye and radioactive injection, an additionial injection of Sienna+ is administered into the breast close to the tumour or nipple (an additional Sienna+ injection is only required if the MRI was undertaken over 24hours prior to surgery). During surgery, the sentinel nodes will be detected with the normal detector (gamma probe), the magnetometer (SentiMag) and visually (blue and black-brown colour). The detected nodes will be excised and are taken to the University of Twente for ex-vivo MRI scanning and quantitative magnetometer measurements. Ex-vivo means that the nodes are already outside your body at the moment of scanning, so the patient is not involved in this procedure. After the ex-vivo MRI, the lymph nodes are send to the Histopathology Laboratory for analysis. The analysis in the laboratory is performed routinely and does not form part of this study.

Study burden and risks

As already mentioned in section E9, there is the risk of tattooing of the skin following injection of Sienna+. However, this is a prevalent problem with the use of blue dye and not with the use of a magnetic tracer. In the previous SentiMag studies (section 1.3 and section 1.4 in protocol), we used a magnetic dye that is similar to Sienna+, called Endorem. Injection of Endorem resulted in minimal skin discolouration in only 6 out of 51 patients.

A potential risk might be the chance of developing adverse reactions to Sienna+. However, the available evidence on the use of similar materials to Sienna+ (for example Resovist, when only less than 1% of patients developed adverse reactions to intravenous injection of the dye in much higher concentrations) and the CE marking of Sienna+ show that there are no additional risks to participants other than the discolouration / staining noted previously with Endorem.

Sienna + has been reviewed and tested as specified in EN 10993-1:2009 based on the specified site of injection and showed no serious reaction after injection.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with breast cancer scheduled for SLNB and who are clinically and radiologically (pre-operative ultrasound normal or indeterminate/abnormal and benign FNA or core biopsy) node negative;Patients available for follow-up for at least 12 months

Exclusion criteria

Intolerance / hypersensitivity to iron or dextran compounds or Sienna+;Patients who cannot / do not receive radioisotope for SLNB;Patients with an iron overload disease;Patients with pacemakers or other implantable devices in the chest-wall;Intolerance / hypersensitivity to patent blue dye in centres where this is used routinely;Exlusion criteria MRI-subprotocol:;Presence of implantable devices (electronically, magnetically, mechanically

activated. E.g: cardioverter defibrillators, cardiac pacemakers);Metallic splinters in the eye;Ferromagnetic haemostatic clips in the central nervous system;Claustrophobia

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-05-2012
Enrollment:	75
Type:	Actual

Medical products/devices used

Generic name:	Sienna+ and SentiMag
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	10-04-2012
Application type:	First submission
Review commission:	METC Twente (Enschede)
Approved WMO Date:	30-08-2012
Application type:	Amendment
Review commission:	METC Twente (Enschede)

Approved WMO Date:	24-09-2013
Application type:	Amendment
Review commission:	METC Twente (Enschede)
Approved WMO Date:	28-01-2014
Application type:	Amendment
Review commission:	METC Twente (Enschede)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL39018.044.11