MEthods for LOcalization of Different types of breast lesions

(EUBREAST 4)

A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions

Intergroup Study EUBREAST – iBRA-NET

NCT 05559411

Study Protocol

Version 1.0
18.09.2022

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2. Glossary and Abbreviations

BC	Breast cancer
DCIS	Ductal carcinoma in situ
IOUS	Intraoperative ultrasound
MRI	Magnetic resonance imaging
RCT	Randomized controlled trial
RFID	Radiofrequency identification
ROLL	Radioguided occult lesion localization
RRL	Radar reflector-localization
RSL	Radioactive seed localization
WGL	Wire-guided localization

3. Rationale

In the last decades, the proportion of breast cancer (BC) patients receiving breast-conserving surgery has increased steadily, reaching 70-80% in developed countries [1-3]. Since positive resection margins are strongly associated with local recurrence risk, the goal of breast surgery is the complete tumor removal and most national and international guidelines recommend re-operation, either in form of re-excision or mastectomy, until clear margins have been reached [4]. Re-operation rates vary widely, with population-based studies reporting a range of 15-35%, and the necessity for a second surgery can lead to increased patient anxiety, a delay in start of adjuvant treatment, worse cosmetic outcome and increased complication rates and costs [1,5-9]. Therefore, re-operation rate has been included as a quality indicator in several countries [10].

Several imaging-guided techniques have been developed to guide removal of non-palpable breast lesions, the oldest one being preoperative wire placement under ultrasound or mammographic guidance, usually followed by radiography or ultrasound of removed tissue [11]. Newer techniques, such as intraoperative ultrasound (IOUS), radioguided occult lesion localization (ROLL), radioactive seed localization (RSL), radar reflector-localization (RRL), magnetic localization, and radiofrequency identification (RFID) tags have been introduced as an alternative to wire-guided localization (WGL) [12,13].

To date, comparative data on the rates of successful lesion removal, negative margins and re-operations in patients undergoing different localization techniques are limited. In case of RSL and ROLL, several randomized controlled trials (RCTs) have been conducted, usually comparing these methods to WGL [11]. Regarding IOUS, results from three RCTs with WGL as control arm are available [14-16]. For the other markers that require a special probe to guide intraoperative detection, i.e., magnetic markers, radar reflectors and RFIDs, only data from prospective and retrospective cohort studies are available, which makes a direct comparison between different techniques challenging [17-20]. Further, since some of these studies were funded by the manufacturer of the marker examined, a potential bias cannot be excluded. In the vast majority of the available studies, the patient's perspective with regard to discomfort and pain level has not been evaluated.

The aim of the proposed study is to comparatively evaluate different imaging-guided localization methods used for surgical removal of non-palpable malignant breast lesions with regard to oncological safety and patient-reported outcomes.

4. Methods

4.1. Study design

Non-interventional observational international prospective cohort study
Investigator-initiated study

4.2. Aims and objectives

Primary outcomes:

- Intended target lesion and/or marker removal, independent of margin status on final histopathology
- Negative resection margin rates (defined as lesion removal with no invasive or non-invasive carcinoma on ink) at first surgery

Secondary outcomes:

- Rates of second surgery
- Rates of secondary mastectomy
- Resection Ratio, defined as actual resection volume divided by the calculated optimum specimen volume
- Duration of surgery in BC patients, defined as time between first incision and end of skin closure (patients receiving simultaneous reconstructive, oncoplastic or contralateral surgery will be excluded from this analysis)
- Marker dislocation rates
- Rates of marker placement failure, i.e., marker dislocation requiring a placement of a second marker
- Rates of localization failure, i.e., failed removal of marker or lesion, or necessity to switch to another intraoperative localization method
- Comparison of patient-reported outcomes (e.g., patient's discomfort, pain level, and impairment of breathing)
- Comparison of diagnostician/radiologist's satisfaction with marking technique
- Comparison of surgeon's satisfaction with localization technique
- Rates of "lost markers" (defined as markers placed prior to surgery and not retrieved at surgery)

- Volume and weight of resected tissue
- Impact of experience of study sites on other outcome measures, depending on the localization technique used
- Impact of self-reported ethnicity on other outcome measures
- Evaluation of surgical standards of care in different countries
- Evaluation of economic resources required for different localization techniques (material costs, operative time etc.)
- Evaluation of MRI artifacts
- Evaluation of complication rates related to marker placement
- Evaluation of perioperative complication rates

4.3. Inclusion and exclusion criteria

Inclusion criteria

- Signed informed consent form
- Malignant breast lesion requiring breast-conserving surgery and imaging-guided localization (either DCIS or invasive breast cancer; multiple or bilateral lesions and the use of neoadjuvant chemotherapy are allowed)
- Planned surgical removal of the lesion using one or more of the following imaging-guided localization techniques:
    - Wire-guided localization
    - Intraoperative ultrasound
    - Magnetic localization
    - Radioactive seed localization
    - Radioguided Occult Lesion Localization (ROLL)
    - Radar localization
    - Radiofrequency identification (RFID) tag localization
    - Ink/carbon localization
- Female / male patients ≥ 18 years old

Exclusion criteria

- Patients not suitable for surgical treatment
- Patients requiring mastectomy as first surgery
- Surgical removal without imaging-guided localization

4.4. Registration and therapy

All patients with invasive or in situ breast cancer scheduled for a breast-conserving surgery and requiring imaging-guided localization should be informed about the possible participation in the MELODY study. The inclusion and exclusion criteria are verified by the investigator and written informed consent is obtained from the patient.

Surgical treatment, pathological assessment and postoperative locoregional and systemic therapy should be conducted according to institutional and national standards. Since the MELODY study in a non-interventional trial, the Study Sites do not deviate from their own institutional protocol at any timepoint.

Diagnostician/radiologist's and Surgeon's satisfaction with the marking and localization technique used are assessed using a short questionnaire.

Patient-reported outcomes are reported using a short questionnaire (to be completed between localization/surgery and postoperative visit).

Patients will be followed for 30 days postoperatively for perioperative complications. No long-term surveillance is required.

4.5. Quality assurance

To ensure consistent quality in localization and excision, the Study Site must have completed a minimum of 5 excisions using the localization device/method before enrolling patients in the respective cohort.

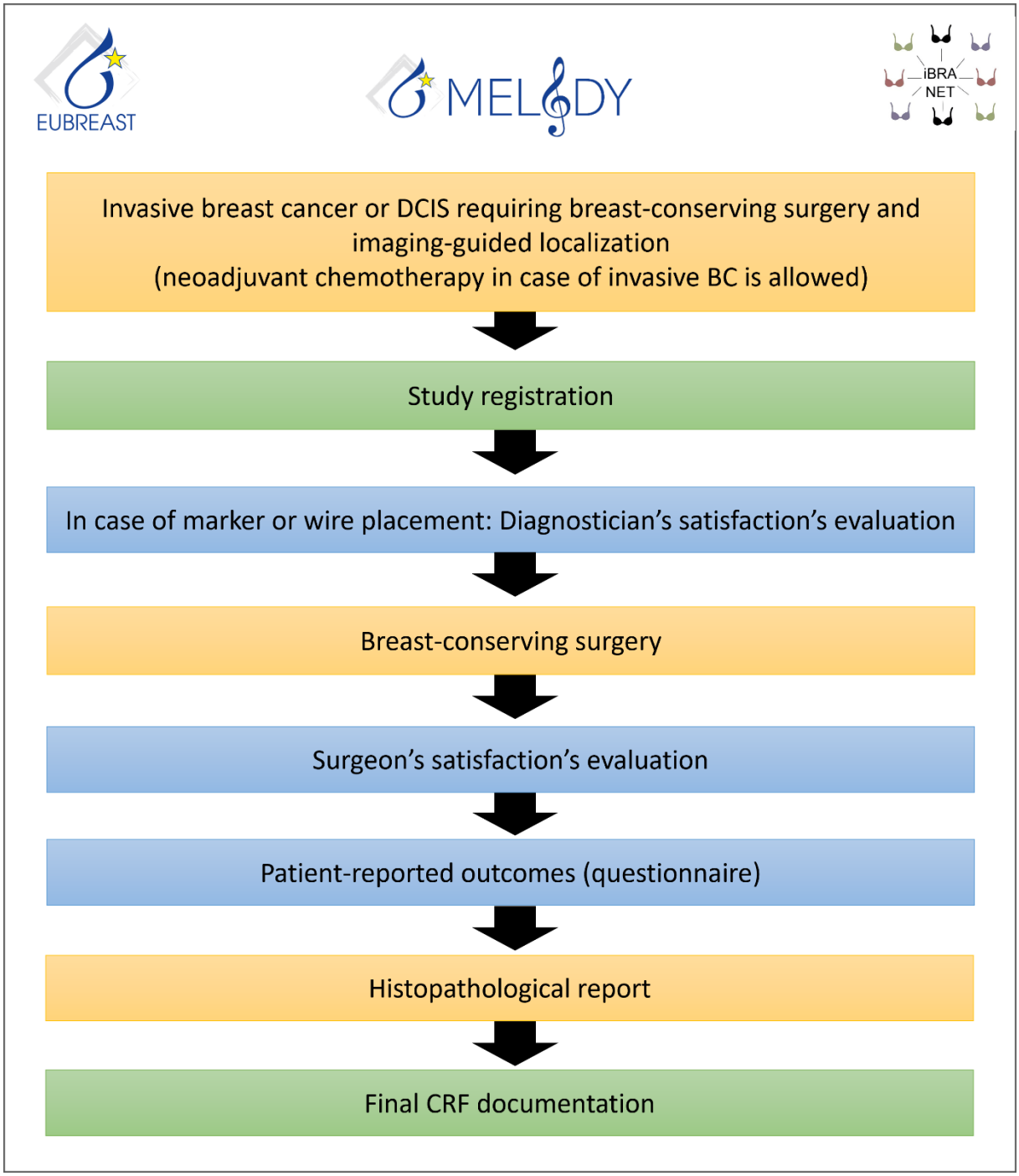
4.6. Target accrual

7416 patients

4.7. Study duration

2 years

Study flow chart



5. Data management

This part of the Protocol will discuss the Data Sharing and Data Management policy between two parties: The Provider & The Recipient. The Provider as per this agreement will be the Study Site supplying the dataset in accordance with the Protocol of the study. The Recipient will be the EUBREAST Study Group who will collect the data in accordance with the Data Protection policy as set out in this agreement. Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the server belonging to and managed by EUBREAST.

To register for the study, Study Sites (Providers) will contact the Head of their National Steering Committee to request participation in the Study and access to the online database. Each Study Site will then be designated a Site ID in format: Two-letter Country Code – Site number (e.g., DE-001 for the first German Study Site), which will be used as a prefix for the Patient ID (e.g., DE-001-001 for the first patient recruited at Study Site DE-001). All patients who consent to participation in the Study are recorded in the Subject Identification Log that remains at the study site. This document is the only record containing patient personal data and the corresponding Patient ID. EUBREAST does not have access to the Subject Identification Log at any time. No personal data will be disclosed under the Data Sharing Agreement. No patient identifiable data will be recorded for the purpose of the Study.

For further analysis data are filled in the REDCap-based eCRF by the Study Site. The printed version of CRF (PDF file) is also available. Its use is optional. All data are checked for plausibility through remote monitoring. The Monitors do not have access to patient data and do not visit Study Sites. Are the data insufficient for evaluation of predefined study aims, the Monitor will generate a query and Study Site will be requested to clarify.

REDCap has been disseminated for local use by more than 1,005 academic/non-profit consortium partners in 79 countries. Vanderbilt leads the REDCap Consortium, which currently supports more than 99,000 projects and 128,000 users. More information about the consortium and system security can be found at http://www.projectredcap.org/. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

REDCap is created by Vanderbilt University, with the server hosted by the EUBREAST. REDCap was developed specifically around HIPAA-Security guidelines. Web browser communication to the server is SSL-encrypted by default. All other ports are firewall protected.

Data is stored in MySQL databases on a separate server. This server is behind a firewall and can only be accessed from the IP address of the web server. An SSL-tunnel encrypts communication between the web and databases servers. File upload is secured between servers using theWebDAV protocol with SSL. "At rest" encryption is in place on the database server (aes-xts-plain64:sha256 with 512-bit keys). Daily back-ups are made of both servers and stored for two weeks prior to being deleted. Operating security updates are installed automatically. Antivirus software runs to a scheduled protocol on the web server. User passwords are managed directly. Accounts are disabled after 5 failed login attempts. Users are auto logged out after 30 mins of no activity. Daily audit tracking of users is in place with removal of unused user accounts.

5.1. Data Purpose

The Recipient will have access to the Data Set to the extent necessary for the purpose of the Study. The pseudonymized Data Set shall be made available only to the Party responsible for Statistical Analysis. The Data Set will not be disclosed, transferred, or made available to any other third party. Summary Safety data may be transferred to the Manufacturers; however, this will NOT include any personal patient data. The Data Set will be kept confidential, and all reasonable steps will be taken to protect it against accidental or unlawful loss, modification or destruction, or unauthorized access, disclosure, copying, use, misappropriation, or modification. Following study closure, datasets cannot be transferred to any third party without the permission of the Recipient.

The results will be published in an academic publication. The Study Sites will be informed about the publication, and the publications will be uploaded to the EUBREAST and iBRA-NET websites, the link to this publication will be sent to Study Sites. In accordance with customary scientific practice, any publications or presentations made in relation to the results, whether in oral, visual, or written form, the Study Site will be acknowledged as the source of the Data Set (see section “Publication and authorship policy”).

5.2. Data Ownership

The data is submitted by the Provider with the intention of contributing to a combined dataset. Providers can access their Study Site’s complete dataset at any point within the study recruitment period.

6. Publication and authorship policy

All presentations and publications will be made on behalf of the EUBREAST and iBRA-NET Study Groups. Two levels of authorship are proposed based on degree of study participation:

6.1. Named authors

Named authors will be required to meet the International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship. These will include:

- Principal Investigator and Deputy Principal Investigator
- Members of the International Steering Board
- Heads of National Steering Committees representing countries with top recruiter status
- Main statistician

6.2. Acknowledged collaborators

Collaborators will have made a considerable contribution to the study but will not have met the ICMJE criteria for authorship (non-author contributors). These will include:

- Heads of National Steering Committees representing countries without top recruiter status
- Members of National Steering Committees
- Local PIs of active Study Sites who have recruited at least ten study participants. Recruitment in this context includes submission of at least 10 completed data sets.

All acknowledged collaborators will be listed as MELODY Study Group.

7. Statistical considerations

The study is defined as a non-inferiority study with two primary endpoints and six comparisons for each endpoint. Each localization device/method will be compared to the wire-guided localization considered standard. To keep an overall type 1 error of 5%, each of the 12 comparisons will be made with an alpha of 0,417%. The first co-primary endpoint is the intended lesion removal. The failure rate of WGL in the literature is 0.6%, giving an identification rate of 99.4% [11]. A clinically significant difference between techniques was considered to be less than 1.1% (non-inferiority margin). Given an allocation rate of 2:1 for WGL : experimental group, sample sizes of 1854 in the WGL group and 927 in each experimental group are sufficient to show non-inferiority with a power of 80%. The other co-primary endpoint is the positive margin rate. The positive margin rate of WGL in the literature is 15%, giving a negative margin rate of 85% [21]. A clinically significant difference between techniques was considered to be less than 5% (non-inferiority margin). With the given sample sizes, non-inferiority with respect to margins can be shown with a power of 80.04%. Each commercially available device will be analyzed in a separate cohort.

Further, a pooled analysis of the MELODY data with data from iBRA-NET audits is planned.

8. Safety

MELODY is a non-interventional study. All diagnostic and therapeutic procedures will be conducted according to national and institutional standards in the clinical routine. One of the secondary endpoints of the study is the evaluation of safety of different types of lesion localization, particularly with regard to lost marker rates and localization failure.

9. Funding

Study support is currently applied for.

10. References

1. DKG. Annual Report 2020 of the Certified Breast Cancer Centres (BCCs), Audit year 2019 / indicator year 2018. Publisher: Deutsche Krebsgesellschaft / German Cancer Society, Berlin, Germany, in cooperation with OnkoZert, Neu-Ulm, Germany. 2020, DOI:
2. Chen K, Li S, Li Q et al. Breast-conserving Surgery Rates in Breast Cancer Patients With Different Molecular Subtypes: An Observational Study Based on Surveillance, Epidemiology, and End Results (SEER) Database. Medicine (Baltimore) 2016; 95: e2593
3. Morrow M, Abrahamse P, Hofer TP et al. Trends in Reoperation After Initial Lumpectomy for Breast Cancer: Addressing Overtreatment in Surgical Management. JAMA Oncol 2017; 3: 1352-1357
4. Houssami N, Macaskill P, Marinovich ML et al. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol 2014; 21: 717-730
5. Fisher S, Yasui Y, Dabbs K et al. Re-excision and survival following breast conserving surgery in early stage breast cancer patients: a population-based study. BMC Health Serv Res 2018; 18: 94
6. Monaghan A, Chapinal N, Hughes L et al. Impact of SSO-ASTRO margin guidelines on reoperation rates following breast-conserving surgery. Am J Surg 2019; 217: 862-867
7. Xue DQ, Qian C, Yang L et al. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. Eur J Surg Oncol 2012; 38: 375-381
8. Wazer DE, DiPetrillo T, Schmidt-Ullrich R et al. Factors influencing cosmetic outcome and complication risk after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol 1992; 10: 356-363
9. Pataky RE, Baliski CR. Reoperation costs in attempted breast-conserving surgery: a decision analysis. Curr Oncol 2016; 23: 314-321
10. Tamburelli F, Maggiorotto F, Marchio C et al. Reoperation rate after breast conserving surgery as quality indicator in breast cancer treatment: A reappraisal. Breast 2020; 53: 181-188
11. Chan BK, Wiseberg-Firtell JA, Jois RH et al. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev 2015, DOI: 10.1002/14651858.CD009206.pub2: CD009206
12. Rubio IT, Henry-Tillman R, Klimberg VS. Surgical use of breast ultrasound. Surg Clin North Am 2003; 83: 771-788
13. Layeequr Rahman R, Puckett Y, Habrawi Z et al. A decade of intraoperative ultrasound guided breast conservation for margin negative resection - Radioactive, and magnetic, and Infrared Oh My. Am J Surg 2020; 220: 1410-1416
14. Hu X, Li S, Jiang Y et al. Intraoperative ultrasound-guided lumpectomy versus wire-guided excision for nonpalpable breast cancer. J Int Med Res 2020; 48: 300060519896707
15. Hoffmann J, Marx M, Hengstmann A et al. Ultrasound-Assisted Tumor Surgery in Breast Cancer - A Prospective, Randomized, Single-Center Study (MAC 001). Ultraschall in Med 2019; 40: 326-332
16. Rahusen FD, Bremers AJ, Fabry HF et al. Ultrasound-guided lumpectomy of nonpalpable breast cancer versus wire-guided resection: a randomized clinical trial. Ann Surg Oncol 2002; 9: 994-998
17. Gera R, Tayeh S, Al-Reefy S et al. Evolving Role of Magseed in Wireless Localization of Breast Lesions: Systematic Review and Pooled Analysis of 1,559 Procedures. Anticancer Res 2020; 40: 1809-1815
18. Lowes S, Bell A, Milligan R et al. Use of Hologic LOCalizer radiofrequency identification (RFID) tags to localise impalpable breast lesions and axillary nodes: experience of the first 150 cases in a UK breast unit. Clin Radiol 2020; 75: 942-949

19. McGugin C, Spivey T, Coopey S et al. Radiofrequency identification tag localization is comparable to wire localization for non-palpable breast lesions. Breast Cancer Res Treat 2019; 177: 735-739
20. Kasem I, Mokbel K. Savi Scout(R) Radar Localisation of Non-palpable Breast Lesions: Systematic Review and Pooled Analysis of 842 Cases. Anticancer Res 2020; 40: 3633-3643