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

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1. Study administration

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Signatures

Prof. Dr. Maggie Banys-Paluchowski

Principal Investigator

Lübeck, 9.05.2024

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.

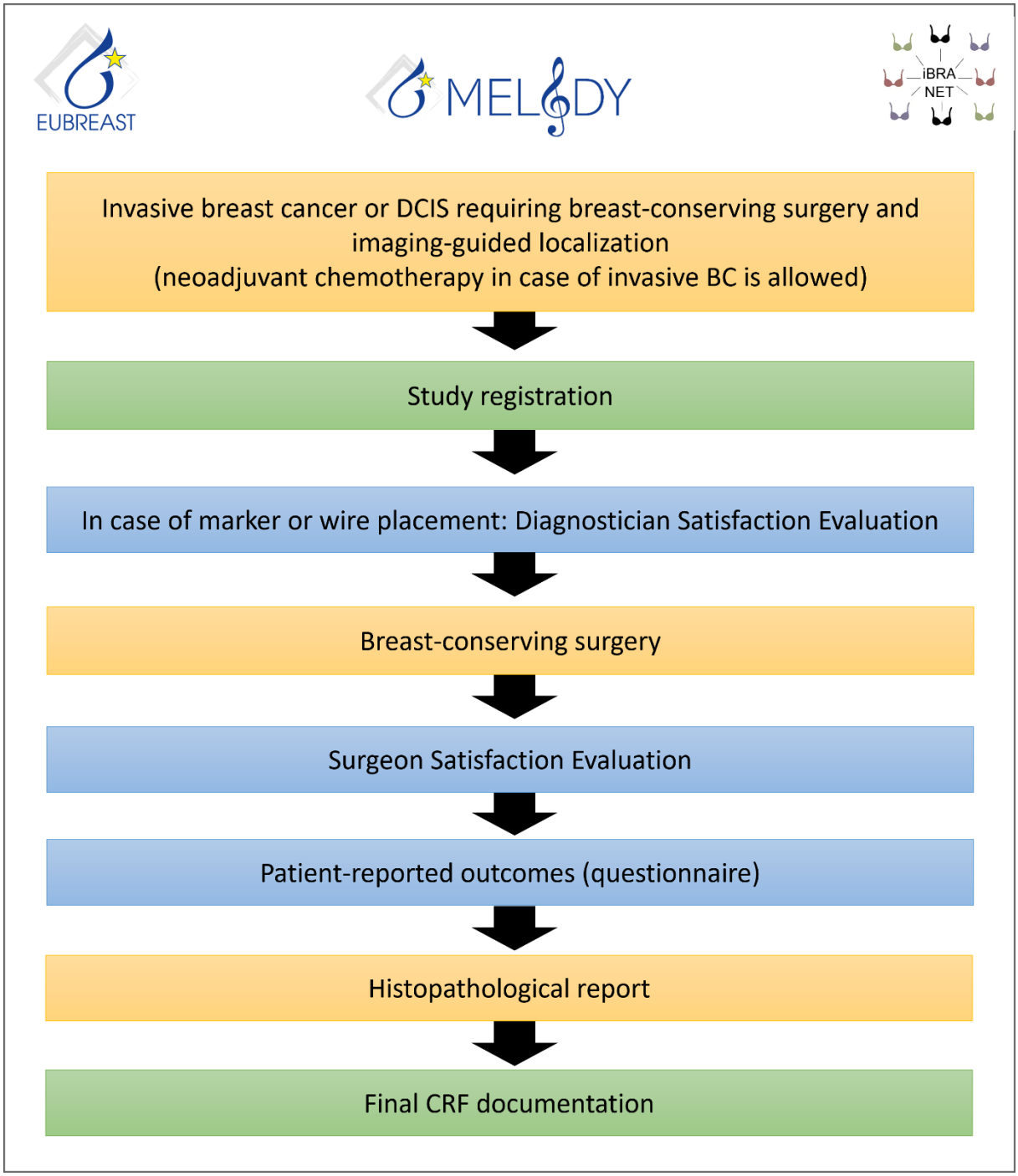
4.6. Target accrual

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

7.1. Sample size consideration

This prospective non-interventional study is designed to evaluate and compare the performance of 6 imaging-guided techniques with wire-guided localization (WGL). It is hypothesized that the imaging-guided methods perform better or equal to WGL in terms of the likelihood of the intended lesion removal, as well as the likelihood of a negative margin. Each localization device/method will be compared to the wire-guided localization considered standard using propensity scoring. 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 difference of 1.1% between techniques is considered to be clinically significant. 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 restrict the upper boundary of the respective confidence interval for the differences in identification rates of WGL versus experimental device to 1.1% 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%, yielding a negative margin rate of 85%, respectively [21]. A clinically significant difference between techniques was considered to be less than 5%. Assuming that each experimental method also has a negative margin rate of 85%, the upper limit of the confidence interval for the difference in negative margin rates is limited to 5% with a power of 80.04%. Each commercially available device will be analyzed in a separate cohort. To adjust for multiplicity and to keep an overall type 1 error of 5%, each of the 12 comparisons are planned with an alpha of 0.417%.

7.2. Planned statistical analyses

This prospective cohort study has two independent primary endpoints A and B which will be tested 6 times each to compare each of the imaging-guided techniques separately with wire-guided localization as the gold standard. To control the family-wise error rate at 5% for the 12 tests, a Holm-Bonferroni procedure will be applied.

Endpoint A

Rate of intended target lesion and/or marker removal, independent of margin status on final histopathology, to be compared between imaging-guided techniques and WGL.

Hypotheses:

H10: $P1_{exp\_i} - P1_{WGL} \leq -0.011$ versus

H11: $P1_{exp\_i} - P1_{WGL} > -0.011$,

with $P1_{exp\_i}$, $P1_{WGL}$ being the intended lesion rates in the *i*th experimental group and in WGL group.

Endpoint B

Rate of negative resection margin rates (defined as lesion removal with no invasive or non-invasive carcinoma on ink) at first surgery, to be compared between imaging-guided techniques and WGL.

Hypotheses:

H20: $P2_{exp\_i} - P2_{WGL} \leq -0.05$ versus

H21: $P2_{exp\_i} - P2_{WGL} > -0.05$,

with $P2_{exp\_i}$, $P2_{WGL}$ being the negative resection margin rates in the *i*th experimental group and in WGL group.

To balance the baseline variables between treatment groups, inverse-probability-of-treatment-weighting (IPTW) is applied to each pairwise comparison. Variables used for balancing include those variables that are associated with the outcome. The IPT weights will be considered for all primary endpoint comparisons.

Analysis of the primary endpoints:

The difference of the rates between the groups (WGL – experimental group *i*) will be calculated and compared to the respective margin. The null hypothesis is rejected, if the lower bound of a defined confidence interval increases the margin.

To define the width of each confidence interval, the Holm-Bonferroni method will be applied:

1. Step: t-tests between each experimental method and WGL will be applied.
2. Step: The hypotheses are ordered by their nominal p-values. Only hypotheses indicating that the effectiveness of imaging-guided technique exceeds WGL are considered here. If none of the hypotheses shows this trend, the hypotheses are ordered by the lower bound of the 95% confidence interval of the estimated beta, starting with the highest number.
3. Step: For the first hypothesis in this order, a $(100\% - \frac{5\%}{12})$-confidence interval will be calculated. If the lower bound of this confidence interval increases the respective margin, the null hypothesis is rejected, and the next step will be applied. If the lower bound of this confidence interval does not increase the respective margin, the null hypothesis is accepted, and the procedure ends here.

4. Step: For the next hypothesis in this order, a $(100\% - \frac{5\%}{11})$-confidence interval will be calculated, and decisions are made as in the previous step. In each following step, the confidence interval gets incrementally larger, by dividing 5% through the number of untested hypotheses.

Results of secondary outcomes analyses will be interpreted as exploratory. Descriptive statistics of all baseline variables will be calculated by treatment and also after pooling the image-based methods.

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

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11. Protocol Change Log

Version	Changes
1.3	Section “Statistical considerations” extended [no versions between 1.0.18 and 1.3; version number changed to 1.3 to align with version numbers of the German protocol]
1.0.18	List of National Steering Committees updated (Egypt) Title of Dr. Banys-Paluchowski updated Title of Jai Min Ryu updated
1.0.17	List of National Steering Committees updated (Korea)
1.0.16	Signature Page added
1.0.15	Responsibility for data management specified
1.0.14	List of National Steering Committees updated (Pakistan)
1.0.13	List of National Steering Committees updated (Argentina)
1.0.12	List of National Steering Committees updated (Peru)
1.0.11	List of National Steering Committees updated (Greece)
1.0.10	List of National Steering Committees updated (Portugal)
1.0.9	List of National Steering Committees updated (Ireland)
1.0.8	List of National Steering Committees updated (Denmark)
1.0.7	List of National Steering Committees updated (Austria) and responsibility for data management updated (EUBREAST)
1.0.6	List of National Steering Committees updated (Spain)
1.0.5	List of National Steering Committees updated (Sweden, India)
1.0.4	List of National Steering Committees updated (France added)
1.0.3	Affiliation of the Head of National Steering Committee in Italy updated
1.0.2	List of National Steering Committees updated
1.0.1	Protocol Change Log added Representative of the OPBC Prof. Walter Weber added as member of the ISB List of National Steering Committees updated Affiliation of Prof. Kühn updated