Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection – the SENOMAC trial.

A randomized study of patients with sentinel node macrometastasis

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1. Summary

Sentinel node (SN) biopsy in breast cancer has proven to be a reliable method, and several follow-up studies have shown that it is safe to refrain from axillary completion axillary lymph node dissection (ALND) in sentinel node-negative breast cancer. Moreover, SN biopsy alone is associated with significantly less postoperative arm discomfort. Because of the surprisingly low rate of axillary recurrence among patients who have not been subjected to any axillary procedure, as well as among SN-positive patients who have not undergone completion ALND, the role of ALND has increasingly been called into question even among patients who have SN metastases. Two studies have been published in recent years in which SN-positive breast cancer patients were randomized either to undergo completion ALND or not. The first study (ACOSOG Z0011) included patients with SN macrometastases who had breast-conserving surgery. The second study (IBCSG 23-01) included patients with SN micrometastasis. The studies did not demonstrate any difference in the rate of axillary recurrence, and survival was even slightly better among patients who underwent SN biopsy alone, although the difference was not statistically significant. However, these studies had several weaknesses, including low power and especially how patients were selected for the ACOSOG Z0011 study.

This prospective multicenter study includes patients with 1-2 SN macrometastases. Patients are randomized to either undergo ALND or not. The study is designed as a non-inferiority study in which we accept a worsening in breast cancer-specific survival in the experimental arm (no ALND) of at most 2.5% after 5 years. Previous Swedish results show a 5-year breast cancer-specific survival rate of 92% among patients with SN macrometastases. We plan to include 3500 patients to achieve 80% power in being able to detect a potential worsening of the breast cancer-specific 5-year survival rate from 92% among patients who undergo ALND to 89.5% among those who do not. All patients will otherwise primarily be treated according to national clinical guidelines and will be clinically followed yearly for 5 years, after 10 years and finally after 15 years.

2. Background

Lymph node metastasis is one of the factors of greatest prognostic importance in breast cancer [1-3]. Lymph node metastases can be classified as isolated tumor cells (≤ 0.2 mm and/or <200 cells), micrometastasis (> 0.2 but ≤ 2 mm and/or > 200 cells) and macrometastasis (> 2 mm) [4].

Axillary procedures in breast cancer surgery include either axillary lymph node dissection (ALND) or sentinel node (SN) biopsy. The purpose of axillary procedures has been viewed in part as diagnostic to be able to determine adjuvant therapy, and in part therapeutic to diminish/eliminate tumor burden. However, the therapeutic effect has increasingly come into question.

Sentinel node (SN) biopsy has proven to be a reliable method [5], and several follow-up studies have shown that it is safe to refrain from completion ALND in sentinel node-negative breast cancer [6-10]. The greatest advantage to the SN biopsy approach is the significant decrease in the frequency and severity of arm problems since fewer lymph nodes are removed from the axilla [11-14].

Refraining from ALND in cases of SN-negative breast cancer is standard treatment in Sweden and most other Western countries. Completion ALND is currently carried out in SN-positive breast cancer. However, in about 50-65% of patients, no additional metastases are found in the remaining lymph nodes [15], in which case a number of nodes have been unnecessarily surgically removed.

Interestingly, a surprisingly low rate of axillary recurrence has been noted among patients who have not been subjected to any axillary procedure, as well as among SN-positive patients who have not undergone completion ALND [16-22]. In addition, follow-up studies have shown that the incidence of axillary recurrence among SN-negative patients who were not subjected to axillary lymph node dissection is much lower than expected, especially considering the approximately 5-10% false-negative SN rate [5, 9, 18]. These findings suggest that not all metastatic lymph nodes develop into clinically significant metastases. It may be speculated that this is due to the adjuvant therapy, that the body's immune system is fighting the metastases, or that not all metastases have the ability to grow without the presence of a primary tumor.

Consequently many have begun to question the role of ALND in SN-positive cases, and after Giuliano et al. published their ACOSOG Z0011 study in 2011, [23] the strategy of refraining from completion ALND in SN-positive cases has gained more advocates and is now also beginning to be embraced in many places, especially in the US [24, 25]. The ACOSOG Z0011 study randomized SN-positive patients to either undergo ALND or to refrain from the procedure. After a median follow-up period of over six years, no difference in the rate of axillary recurrence was found, and survival was even slightly better among patients who only underwent SN biopsy (disease-free survival 83.9%, compared with 82.2% for patients who underwent ALND), although the difference was not statistically significant. The study has received some criticism [26, 27]. The main objection is that the patients who were included were likely selected. Even though this was an American multicenter study with 177 participating centers, only half of the initially planned 1800 patients were included over a 5-year period. The majority of patients also had favorable prognostic factors, and in regard to the size of SN metastases, the distribution was somewhat skewed between the groups, with more isolated tumor cells and micrometastases in the group that was randomized to refrain from ALND. ACOSOG Z0011 only included patients who underwent breast-conserving surgery and who received postoperative radiotherapy to the entire breast and in whom a maximum of two SNs with metastases were found.

A different study (IBCSG 23-01), in which SN-positive patients were randomized to either undergo completion ALND or not, was published in 2013 [28]. This study included only patients with SN micrometastases, but showed, as did the ACOSOG Z0011, slightly better disease-free survival in the group operated with SN biopsy alone (87.8% compared with 84.4% for those who underwent ALND), though the difference was not statistically significant here either. Neither the ACOSOG Z0011 study nor the IBCSG 23-01 study succeeded in enrolling the planned number of patients and the studies probably do not have sufficiently high power to detect small differences.

Besides the ACOSOG Z0011 study and the IBCSG 23-01 study, only a few other randomized studies compare patients who have undergone axillary lymph node dissection with patients who have not. In the 1970s a total of 1665 women with breast cancer were randomized to have either mastectomy plus axillary lymph node dissection (radical mastectomy), mastectomy with radiotherapy of regional lymph nodes or mastectomy alone with subsequent ALND only in cases of clinical axillary recurrence [20, 21]. No difference in survival was

found after either 10 years or 25 years, but 65 of the 365 patients who received no treatment to the axillary region were subsequently reoperated with ALND when they presented with clinical lymph node metastases. The study was criticized because among many of the patients who did not undergo ALND, multiple lymph nodes were found in the mastectomy material.

In a somewhat more recent study, between 1993 and 2002, in which 473 women over age 60 who were randomized to either undergo ALND or to have no axillary procedure [22], there was no observed difference in survival either. However, this study also failed to meet the enrolment target, and likely included too few patients to be able to find a moderate difference in mortality. In 2012 a review of studies was published comparing SN-positive patients who underwent axillary lymph node dissection with patients who did not [29]. The study concluded that it appears to be safe to refrain from axillary lymph node dissection in selected patients. However, most of the studies included were retrospective, and the majority had only enrolled limited numbers of patients.

Some studies have also shown a higher rate of distant metastases and other cancers among breast cancer patients who underwent ALND, and it has been speculated that lymph node removal may put people at an immunological disadvantage. [10].

There are, however, a few studies that suggest that axillary lymph node dissection may still have some therapeutic benefit. A meta-analysis predating consideration of sentinel nodes showed that patients who underwent ALND had better survival than those who did not [30]. Similar results were found in a retrospective study comparing ALND with axillary lymph node sampling combined with radiotherapy [31]. In yet another retrospective study, the rate of axillary recurrence among SN-positive patients who did not undergo ALND was a striking 2.0% after just 30 months, despite otherwise favorable prognostic factors (compared with 0.4% among those who underwent completion ALND) [32]. The results from the Dutch MIRROR study [33] also warrant some caution since the rate of axillary recurrence was more than twice as high among patients with SN micrometastases who did not undergo ALND compared with SN-negative patients (5.6% vs 2.3% after 5 years).

In Sweden, most patients with SN macrometastases receive radiotherapy of the axillary region. Several studies have shown that the survival rate among patients who received only radiotherapy was as high as among patients who underwent ALND [20, 34, 35]. A large European study (AMAROS) randomizing over 1400 SN-positive patients, of whom 861 with SN-macrometastases, to either undergo completion ALND or to have axillary radiotherapy

was recently published [36]. No difference in disease-free or overall survival was found. The pre-publication data from this trial have already prompted the UK to approve axillary radiotherapy in lieu of axillary lymph node dissection.

Although the body of findings suggests that axillary lymph node dissection for SN-positive cases is unlikely to significantly improve prognosis, whether there is currently sufficient evidence to begin to routinely refrain from ALND remains uncertain. Further studies are needed, and this prospective multicenter trial will provide a meaningful contribution to answer the question of whether it is safe to refrain from completion ALND. This study will also clarify whether patients can forgo ALND even with mastectomy.

3. Purpose

The main purpose of this study is to evaluate whether it is safe to refrain from completion axillary lymph node dissection in breast cancer cases with SN-macrometastasis. We also want to investigate whether the potential risks of refraining from ALND differ among various subgroups. A secondary aim is the evaluation of arm morbidity, health economic outcome and quality of life in comparison between the two groups.

4. Hypothesis

Refraining from axillary lymph node dissection among patients with sentinel node macrometastasis will not worsen breast cancer-specific survival by more than a maximum of 2.5% after 5 years.

Refraining from axillary lymph node dissection will improve short- and long-term arm morbidity, improve health-related quality of life and reduce health care costs.

5. Method

This study randomizes patients with macrometastases in at most two sentinel nodes to either undergo completion axillary lymph node dissection or not to have any further axillary surgery.

Patients are registered in a database through an electronic Case Report Form (eCRF) and followed prospectively. Frozen tissue samples from the surgery may be saved and stored on a voluntary basis for future research.

Inclusion criteria

- Patients with primary invasive breast cancer T1-T3
- No palpable lymph node metastases prior to sentinel node biopsy
- Macrometastasis in not more than 2 lymph nodes at sentinel node biopsy (further lymph nodes with micrometastasis or ITC do not result in exclusion)
- Oral and written consent
- Age ≥ 18 years
- Preoperative ultrasound of axilla performed

Exclusion criteria

- Regional or distant metastases outside of the ipsilateral axilla
- Prior history of invasive breast cancer
- Pregnancy
- Bilateral invasive breast cancer, if one side meets exclusion criteria. Patients with bilateral cancers where both sides fulfill all inclusion criteria and no exclusion criteria may, however, not be included for either side.
- Medical contraindication for radiotherapy
- Medical contraindication for systemic treatment
- Inability to absorb or understand the meaning of the study information; for example, through disability, inadequate language skills or dementia.

Preoperative assessment

Preoperative assessment is carried out in accordance with local practice with triple diagnostics. Ultrasound of the axillary region is required and suspected node metastases must be biopsied. Patients with *non-palpable* but 1-2 cytologically and radiologically diagnosed axillary metastasis may undergo SN biopsy and be included. Patients may be planned for

partial mastectomy or mastectomy +/- breast reconstruction (including skin-sparing and nipple-sparing alternatives) as all types of breast surgery are eligible in this trial.

Neoadjuvant treatment

Patients planned for neoadjuvant systemic treatment may be included in this trial in case all inclusion criteria are met. Thus, patients without palpable lymph node metastases may undergo sentinel node biopsy prior to start of their neoadjuvant treatment. In case of up to two macrometastases in the sentinel node biopsy, patients may be randomized and included in this trial. Randomization is recommended to be performed before start of neoadjuvant therapy but must at the very latest take place before the first clinical or radiological response evaluation is carried out. In case of disease progression during neoadjuvant treatment and/or the appearance of palpable lymph node metastases, participation in the trial is discontinued and the reason for study termination recorded in the eCRF. The decision to discontinue participation in the trial should always be discussed at a multidisciplinary team conference.

Participant identification and inclusion

The trial committee recommends that participating centers choose to refrain from perioperative sentinel node assessment with frozen section analysis. This recommendation is rooted in both logistical and ethical concerns. Diagnostic procedures during ongoing surgery would mean that 1) a large number of patients who may potentially be eligible for inclusion would need to be informed about the study during presurgical care planning, without subsequently meeting the inclusion criteria (i.e., not having macrometastasis in the SN) and 2) patients whose SN frozen sections show macrometastasis will ultimately be included and randomized while under general anesthesia. However, units that choose for various reasons to proceed with frozen section analysis may still participate in the study (see option 2 below).

Yet another reason to refrain from frozen section analysis involves the currently ongoing national cohort study in which patients with SN micrometastasis may be included, and thereby refrain from completion axillary lymph node dissection after the SN procedure. Preoperative information about inclusion in *two* possible studies, both of which involve patients scheduled for breast cancer surgery with sentinel node biopsy as target groups, may be experienced as unreasonably overwhelming for a patient facing cancer surgery.

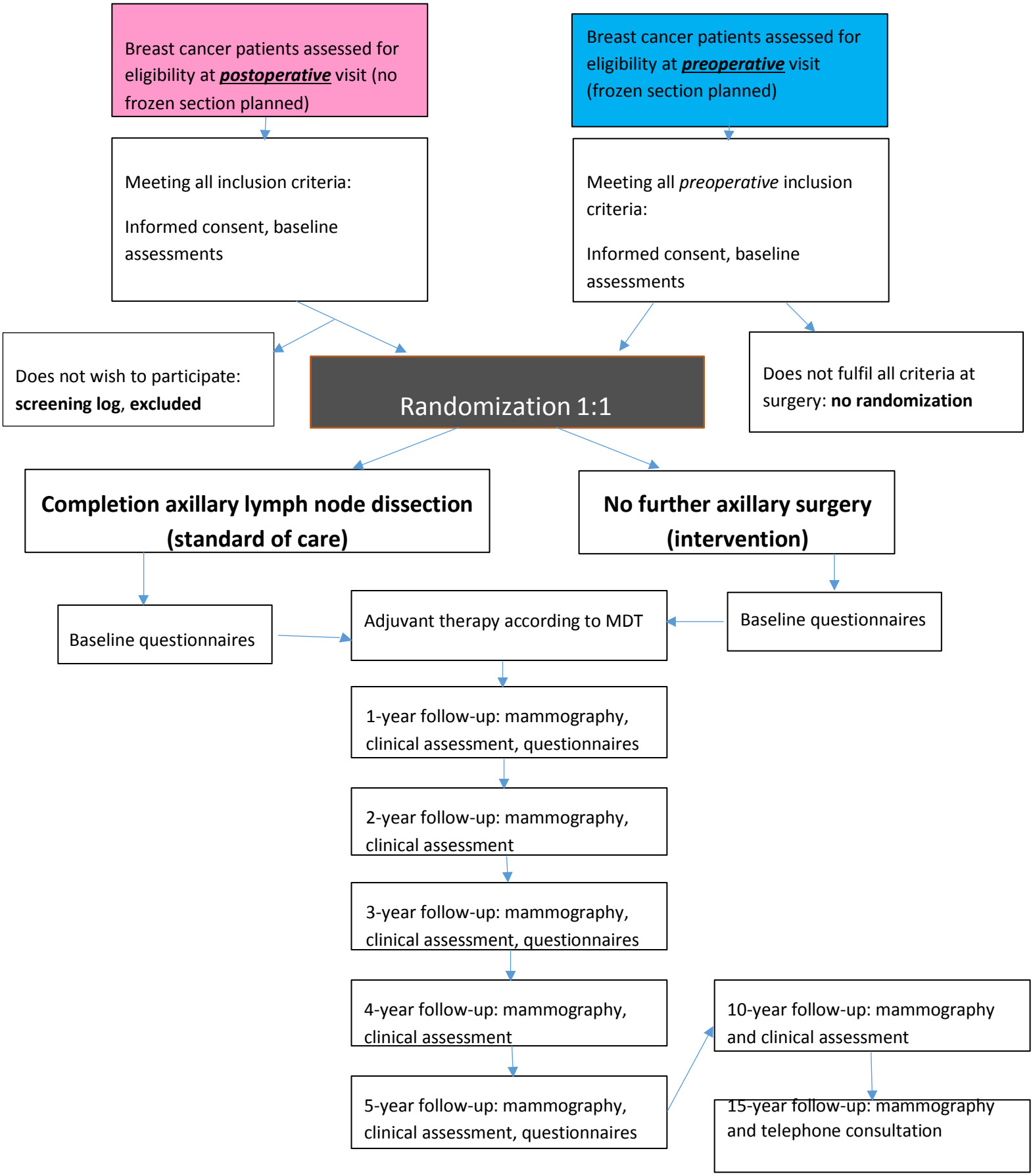
Refraining from frozen section analysis may also free up both surgery and pathology resources, but is estimated to lead to about a 10-12% reoperation rate among those patients who either choose not to participate in the current study, and then undergo completion axillary lymph node dissection, or those who are randomized to this procedure.

Thus, there are two options for the inclusion process (see trial flow chart):

1. Units that do ***not*** perform SN frozen section analysis: patients who meet all inclusion criteria do not receive oral and written information (see enclosed patient information) until after sentinel node biopsy, once the final histopathological results become available. Patients who agree to participate sign the informed consent form and are then randomized. Patients who are randomized to axillary lymph node dissection undergo this procedure in a second surgery. In case of neoadjuvant treatment, this second axillary surgery is performed at the same time as the breast surgery.
2. Units that do perform SN frozen section analysis: patients who meet all other inclusion criteria (except for SN macrometastasis) receive oral and written information (see enclosed patient information) during the planning phase for the primary surgery. Patients who agree to participate sign the informed consent form. If the frozen section shows SN macrometastasis the patient is randomized during the ongoing surgery. Patients who are randomized to axillary lymph node dissection undergo this procedure during the same surgery. In the event that SN macrometastasis is not identified until the final histopathology results are received, the patient may be included in accordance with option 1. In case of neoadjuvant treatment, frozen section is not encouraged as randomization does not lead to an axillary clearance performed at the same session.

In the event that the final histopathology results show that a randomized patient does not meet all criteria (e.g., additional metastasis identified during SN sectioning), the patient must be excluded. In this case, the reason for exclusion is entered in the eCRF to be able to account for attrition in a CONSORT diagram. Patients who fulfil all inclusion criteria and receive information about the trial but are not randomized are registered in screening logs on site. The reasons why these patients were not randomized (declines participation, physician choice, other) are recorded without personal identification number.

SENOMAC trial flow chart (*pre*-and *postoperative* refers to sentinel node biopsy)



Randomization

Randomization may occur on two occasions, see above during “Inclusion”.

1. If frozen section is *not* used the patient is informed and provides consent at the postoperative follow-up visit after sentinel node biopsy/primary surgery, and randomization is carried out during that same visit.
2. If frozen section is used the patient is informed and provides consent prior to the primary surgery. The patient is only randomized during the ongoing surgery if the frozen section shows SN macrometastasis.

At the time of inclusion, inclusion and exclusion criteria are entered into the randomization application, which is a web-based instrument (ALEA). Username and password are required to log in; each researcher authorized to register patients has a personal login user name and password. If all criteria are met, patients are randomized and the treatment to which the patient is allocated is recorded in the patients’ medical file. Randomization is done 1:1 and treatment arms are stratified per country. Randomization is based on permutated block technique.

Injection of isotope and/or blue dye

Injection of isotope and/or blue dye is carried out in accordance with local practice and can be administered intracutaneously above the tumor, around the tumor or as a periareolar injection. Imaging is optional. New methodologies that may be introduced as routine procedure during the course of the study are also permitted, provided that its reliability is proven with a high evidence level. Approval of new methods can only be granted by the study steering committee, which consists of the principal investigators and the adjunct steering group (see title page). Accordingly, the use of Sienna+ and the SentiMag probe, as well as fluorescent dye indocyanine green, has been approved by the steering committee in 2015 and 2016, respectively. Participating centers cannot on their own authority include patients with a sentinel node that was identified by non-approved detection methodology.

Surgical procedure

Sentinel node biopsy is carried out following injection of isotope and/or blue dye into the

ipsilateral breast. Sentinel nodes are identified using a Geiger counter and can be defined as nodes that are blue and/or radioactive. No more than four sentinel nodes should be removed. The sentinel node method includes the palpation of axillary lymph nodes during surgery, and the removal of clearly suspicious lymph nodes which are included in the sentinel node biopsy. Sentinel node frozen section is optional, see under "inclusion" above. In the event that extensive axillary metastatic disease is suspected during surgery, it must be verified by frozen section and in such cases axillary lymph node dissection must be carried out during the same surgical session, and the patient cannot be included in the study.

Patients with failed localization are not eligible for the trial.

Axillary lymph node dissection, when necessary, is conducted at levels I and II with the aim of removing at least ten lymph nodes in total, i.e. including nodes removed at sentinel node biopsy.

Both partial mastectomy and mastectomy are eligible breast surgical interventions, as well as primary breast reconstruction (including skin- or nipple-sparing options). Negative surgical margins are to be achieved.

Pathology

The sentinel node and primary tumor should be examined in accordance with the Society of Pathology Quality and Standardization Committee guidelines in the Swedish KVAST document. These guidelines follow the international classification guidelines by the American Joint Committee on Cancer (AJCC) which should be applied in other countries joining this trial [37]. Tumor characteristics are documented according to standard procedure and should include size, histological type, hormone receptor status, HER2-neu status, proliferation and tumor grade. Lymph node metastases, if any, are measured and classified according to AJCC, i.e. "the size of a tumor deposit is determined by measuring the largest dimension of any group of cells that are touching one another (confluent or contiguous tumor cells), regardless of whether the deposit is confined to the lymph node, extends outside the node (extranodal extension), is totally present outside the lymph node and invading adipose, or is present within a lymphatic channel adjacent to the node. When multiple tumor deposits are present in a lymph node, whether ITCs or micrometastases, the size of only the largest contiguous tumor deposit is used to classify the node, not the sum of all individual tumor deposits or the area in which the deposits are distributed."

Frozen and paraffin-embedded tissue samples

This study will continue for an extended period of time and several years will pass before results are available. During this interval, new prognostic and predictive factors will likely continue to be discovered. To reserve the possibility of also examining new factors in our material, paraffin-embedded tissue from the primary tumor and metastases is stored in local biobanks for future investigation.

Frozen tissue samples are prepared from the fresh specimen according to local practices and will then be stored in the respective local biobank. Each center wishing to take part in the collection of fresh *frozen* tissue will apply at and register with the own local biobank.

Adjuvant therapy

Adjuvant systemic therapy should be given in accordance with national guidelines of each participating country.
In women who have undergone breast-conserving surgery, the remaining ipsilateral breast parenchyma must be irradiated. Boost to the tumor bed should be applied according to each country's national guidelines.
Post-mastectomy radiotherapy (PMRT) and radiotherapy to the regional lymph node basins are based on each country's national guidelines. **It is, however, mandatory, that for those participating in this trial, radiotherapy should not be extended or changed based on which arm the patient is randomized to, ie, sentinel node biopsy only should be regarded as a substitute for axillary clearance.**
In Sweden, radiotherapy to regional lymph node basins follows the recommendations of the Swedish National Guidelines available at www.swebcg.se. The regional lymph node target (CTV) is composed of axilla level 2 and 3, interpectoral lymph nodes and supraclavicular fossa (i.e. axilla level 4) which means that level 1 is omitted from the regional lymph node CTV (in practice parts of level 1 will be covered by the tangential beams targeting the breast/thoracic wall). For detailed volume description, please see the target definition at ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. [38] German radiotherapy guidelines as defined by the Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) are accessible at www.ago-online.de. The corresponding references for the Greek [39], Italian and Danish guidelines are

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, www.radioterapiaitalia.it and www.dbcg.dk, respectively.

The exact regional lymph node target is to be reported in the CRF prospectively throughout the trial. Irradiation of internal mammary nodes (IMN) should be handled according to national guidelines of each country and treatment of IMN must be recorded in the CRF.

Fractionation schedule is chosen according to local practice, i.e. 2 Gy/f x 25 over 33-35 days to the breast and regional lymph nodes. A slightly lower total dose to the nodes (~46 Gy) is accepted. Hypofractionated radiotherapy can be chosen, i.e. 2.67 Gy/f x 15-16 over 19 – 22 days. Dose and fractionation is to be reported prospectively.

Data management

All data are registered using an electronic Case Report Form (eCRF) based on the web application Pheedit. Monitoring is performed according to Good Clinical Practice (GCP) guidelines. The eCRF provides data on age, completed surgery, tumor and lymph node characteristics, as well as neoadjuvant and adjuvant therapy. Data are managed by the Clinical Trial Unit at Kliniska Prövningsenheten, Karolinska University Hospital, Stockholm, Sweden. Security is comparable to bank security with encrypted data.

Recorded information is confidential and the database is privacy-protected; i.e., no data can be traced back to the patient in research reports and no unauthorized individuals may have access to the data about individuals in the database. The database will be maintained until further notice (at least 20 years after inclusion of the last patient) and be reported in accordance with the Personal Data Act (PUL, 1998:204). The authority responsible for the database is Karolinska Institutet, Stockholm, Sweden.

The SENOMAC trial is registered at www.clinicaltrials.gov (NCT 02240472).

Monitoring and follow-up

This prospective trial is conducted according to GCP guidelines and monitored by the Clinical Trial Office at Kliniska Prövningsenheten, Karolinska University Hospital. All patients will be followed up with yearly clinical examination, comprising recent medical history and palpation of breast and regional lymph node basins, and mammography for five years.

Each follow-up visit must take place within +/- two months from the randomisation date, and data are to be completed in the eCRF within one month from the follow-up visit. Additional diagnostic measures, e.g. axillary ultrasound, biopsies or other investigations, are carried out according to clinical findings and in agreement between the treating oncological and surgical departments responsible for routine follow-up. In case of suspected axillary recurrence, a CT of the thoracic region is requested in order to define the level of recurrence in the axilla and exclude further metastatic spread. Results from follow-up and mammography conducted outside the study protocol but within +/- two months of the calculated annual follow-up date may be communicated between departments and recorded in the eCRF to avoid unnecessary visits and radiological investigations.

Data concerning the most recent follow-up visit, and any recurrent disease and deaths will be reported through the follow-up eCRF. In case of suspected or confirmed recurrence, all data on the relapse are to be completed within the recurrence module found in the CRF.

The Clinical Trial Office will be monitoring inclusion and exclusion criteria as well as completeness and accuracy of data recorded in the eCRF by regular on-site visits. To this end, participating units will grant access to patient medical files in due time on request. Patients are informed about monitoring procedures and medical file access in the patient information leaflet and grant their consent to these by signing the consent form.

Participating sites that do not adhere to GCP guidelines or to the agreements stated in the contract signed between the medical responsible at the individual site and the Clinical Trial Office may be excluded from this trial.

Study calendar

Time point	*Option 1* *(postop/no frozen section)*	*Option 2* *(preop/frozen section)*
Baseline recordings (preoperative)	----------	Verify eligibility except for sentinel node status Informed consent Record demographics
Surgery		**Randomization**
Baseline recordings (postoperative)	Verify eligibility including sentinel node status Informed consent **Randomization** Record demographics Baseline questionnaires: Arm morbidity and QoL (EORTC QLQ30-BR23, Lymph-ICF), health economics (EQ-5D) Record tumor and lymph node characteristics Record receptor status Report planned radiotherapy	Record tumor and lymph node characteristics Record receptor status Report planned radiotherapy Baseline questionnaires: Arm morbidity and QoL (EORTC QLQ30-BR23, Lymph-ICF), health economics (EQ-5D)
Follow-up 1 year	Assessment of disease recurrence; date of mammography and date of clinical examination. Data on received adjuvant treatment. Questionnaires: arm morbidity, QoL and health economy	
Follow-up 2 years	Assessment of disease recurrence; date of mammography and date of clinical examination.	
Follow-up 3 years	Assessment of disease recurrence; date of mammography and date of clinical examination. Questionnaires: arm morbidity, QoL and health economy	

Follow-up 4 years	Assessment of disease recurrence; date of mammography and date of clinical examination.
Follow-up 5 years	Assessment of disease recurrence; date of mammography and date of clinical examination. Questionnaires: arm morbidity, QoL and health economy
Follow-up 10 years	Assessment of disease recurrence; date of mammography and date of clinical examination.
Follow-up 15 years	Assessment of disease recurrence; date of mammography and date of clinical examination/telephone consultation.

6. Outcomes

Primary outcome

Breast cancer-specific survival at five years.

Secondary outcomes

- Oncological outcomes at 1, 2, 3, 4, 5, 10 and 15 years:
  - local, regional and distant breast cancer recurrence
  - survival (disease-free and overall)
  - contralateral breast cancer
- Arm morbidity at 1, 3, 5 and 10 years
- Quality of life at 1, 3, 5 and 10 years
- Health economic outcomes at 1, 3, 5 and 10 years

Description and definition of outcomes

- **Breast cancer-specific survival** is measured from the date of randomization until the date of death by breast cancer recurrence. Participants without a breast cancer recurrence will be censored at the date of death by other causes or the date of last follow-up if still alive. An isolated ipsilateral in-breast recurrence in a patient who dies without further breast cancer recurrences is not included in the definition of breast cancer death (see also p. 23, Statistical methods).

- A **local recurrence** is a cytologically or histologically proven breast cancer recurrence in the ipsilateral breast, breast skin or chest wall. The date of the pathology report confirming recurrence is the date of local recurrence.
- A **regional recurrence** is a cytologically or histologically proven breast cancer recurrence in regional lymph nodes, i.e. in the supra- or infraclavicular basins, the contralateral axilla, the ipsilateral axilla, interpectoral area or internal mammary (parasternal) nodal basin. The date of the pathology report confirming recurrence is the date of regional recurrence.
- A **distant recurrence** is a recurrence at any other site than above. Here, the date of first diagnosis, be it by radiology, cytology or histopathology, is recorded. Cytological or histopathological confirmation of the recurrence is encouraged.
- **Disease-free survival** is measured from the date of randomization until the date of first recurrence or death. Recurrence-free and alive participants are censored at the time of last follow-up.
- **Overall survival** is measured from the date of randomization until the date of death by any cause. Alive participants are censored at the time of last follow-up.
- **Contralateral breast cancer** is assessed by mammography or other radiological methods and confirmed by cytology or histology. The date of contralateral breast cancer is the date of the pathology report confirming the diagnosis.
- **Arm morbidity** will be assessed by questionnaire completed by study participants by post, online or during the clinic visit preoperatively and after 1, 3, 5 and 10 years. The questionnaire used is the Lymphedema Functioning, Disability and Health Questionnaire (Lymph-ICF) developed by Devoogdt in 2011. Those sites that wish to complement questionnaires with physical measurement of arm volume and/or function may do so after separate ethical application (amendment).
- **Quality of life** will be assessed by questionnaires completed by study participants by post, online or during the clinic visit preoperatively and after 1, 3, 5 and 10 years. Questionnaires comprise the EORTC QLQ-30 and BR-23.
- **Health economic outcomes** will be assessed at 1, 3, 5 and 10 years by the EQ-5D utility scores and by linking trial data to the national registries of Swedish Health Insurance (Försäkringskassan) and The National Board of Health and Welfare (Socialstyrelsen).

7. Statistics and power calculations

Sample size

The goal of the study is to establish that the intervention (no further axillary surgery) is statistically non-inferior to standard of care (completion axillary lymph node dissection, ALND) for the primary endpoint breast cancer-specific survival (BCSS).

Currently, there have only been two studies in which patients with SN metastases were randomized to undergo completion axillary lymph node dissection or not [23, 28]. Both studies showed a slightly higher DFS among patients who did not undergo axillary lymph node dissection (83.9% compared with 82.2%, and 87.8% compared with 84.4%, respectively). A previous Swedish publication showed a 92% BCSS after 5 years in patients with SN macrometastasis [40]. Power calculations are based on Swedish data which may differ from survival outcomes in other countries that may want to participate in this trial, such as other Nordic countries. Therefore, stratification according to country of primary treatment will be performed in case further countries will be joining this trial.

Clinical non-inferiority is in this study defined as a 5-year BCSS not worsened by more than 2.5% when refraining from ALND. To show that the BCSS at five years is not worsened by more than 2.5% (i.e. a 5-year BCSS of 89.5% in the intervention group compared to 92% in the standard of care group - using a one-sided α of 10% and with a power of 80% - a total of 225 breast cancer deaths need to be observed in the study. This corresponds to show that the upper one-sided 90% confidence interval for the hazard ratio (HR: Intervention/Standard of care) falls below 1.33.

It is anticipated that the study will be able to recruit up to 700 patients per year during a 5-year period giving a total sample size of 3500 patients. With allowance for an extra year of follow-up the necessary number of events (225) is expected to be reached. The total study time will be approximately 7 years.

A data monitoring committee consisting of independent experts in oncology and surgery, as well as a statistician, will review the data and carry out one closed interim analysis three years after the date on which the first study patient was randomized, or when 2000 patients

have been included in the study, whichever comes first. The purpose of this interim analysis is to assess the recruitment to the study, the rate of overall breast-cancer related events and to make sure that patients in the intervention group do not appear to fare significantly worse than patients in the standard of care group. The committee may recommend terminating the study if a significant benefit in favour of standard of care for breast-cancer deaths is shown, such that the HR for intervention versus standard of care significantly ($p=0.001$) exceeds 1, or if the recruitment is so low that that the necessary number of events is unlikely to be reached. If the committee determines that it is safe to proceed with the study, the results of the analysis will remain unknown to everyone except the committee members.

Statistical methods

For the primary endpoint breast cancer-specific survival (BCSS), time will be calculated from the date of randomization to the date of breast cancer death (BCD), or for patients still alive to the date of last visit. A breast cancer death will be defined as a death with information of a preceding or concurrent regional or distant recurrence. Isolated ipsilateral in-breast recurrences will thus not count towards BCD. Disease-free survival time will be calculated from the date of randomization to date of loco-regional recurrence, date of distant recurrence, date of second malignancy or date of death, whichever comes first. For event-free patients time will be calculated from the date of randomization to the date of last visit.

Event-specific cumulative incidence rates - taking competing risks into account - will be estimated using non-parametric methods. Differences in time to failure will be tested using the log-rank test. The effect of the intervention on time to failure will be estimated using proportional hazards regression. Both unadjusted analyses and analyses adjusting for potential confounding factors will be performed. Results will be presented as HRs together with 95% confidence intervals (CI) for all outcomes except for the primary, where a two-sided 80% confidence interval will be used to correspond to the primary one-sided test at the 10% level. Results from the BCSS analysis for which non-inferiority was hypothesized will also be presented as a figure showing CIs for the hazard ratio, the non-inferiority margin and non-inferiority p-value.

Non-inferiority will be concluded if the upper limit of the confidence interval for the hazard ratio falls below 1.33.

Longitudinal health-related quality of life data will be analysed using generalized linear models. Results from these analyses will be presented as mean differences and 95% CIs at 1, 3 and 5 years. Test for interactions between treatment and time – indicating a differential effect of treatment over time – will also be performed. Both intent-to-treat analyses and treatment received analyses will be performed for the primary outcome.

All analyses will be performed using StataCorp 2015 (*Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

8. Ethics

The original version of this study protocol has been approved by the Ethics Committee of the Karolinska Institutet, Stockholm (2014/1165-31/1).

Based on older studies, a degree of increased risk for axillary recurrence among individual patients who do not undergo completion ALND cannot be ruled out. However, newer studies, in which patients received adjuvant chemotherapy according to current standards for lymph node-positive patients show no reduction in survival or increased risk of axillary recurrence. Patients will be closely monitored and receive treatment as needed.

This risk must be weighed against the significant benefit of less arm morbidity associated with less aggressive surgery. More and more breast surgeons, in Sweden and abroad, are discussing a desire to abandon ALND in the majority of patients with SN metastasis, and in many places such discussions have led to action. Nevertheless, there is a risk that this approach will be routinely adopted before sufficient evidence is available, for which reason it is crucial to first explore this option through a study.

9. Significance

Since most patients with sentinel node metastasis have no additional metastases, and since previous studies suggest that even metastases left in place do not have a significant impact on prognosis, it is likely that many patients are undergoing an unnecessarily aggressive surgery, which in many cases leads to increased arm morbidity. If we are able to show that it is safe to refrain from axillary lymph node dissection, then a large number of patients will be spared unnecessary suffering.

Refraining from axillary lymph node dissection will also reduce resource needs for surgery, pathology assessment and hospitalization.

10. Withdrawal

Patients who wish to withdraw from the study may do so at any time, without providing a reason. The patient may request to have completion axillary lymph node dissection during the follow-up period. Participants may wish to stop their taking part in the questionnaire part of the study which does not exclude them from the overall study.

Data already included in previous eCRFs will be included in the analysis if the participant does not explicitly wish to have her data excluded from analysis. Ceasing participation will be recorded in the eCRF.

11. Publication policy

Before the collaborative publication of the main oncological outcome from the entire cohort, no other publication regarding oncological outcome on parts of the cohort can be attempted. Each member of the trial committee of each participating country is to be a co-author on any publication reporting on the main findings of the SENOMAC trial, that is, any report on oncological outcome and safety issues. Any subanalysis using data from the SENOMAC trial, such as radiotherapy quality assurance or quality of life, must first get the permission to perform analyses from the trial committee, i.e. all national trial committees if international data are used or the respective national committee if only one country's data are used. The overall coordinating investigator is to be informed and applied to for any publication, whether it regards national or international data. In such publications, the trial committee(s) must be part of the authors' list as the "SENOMAC Trialists' Group"; members of the trial committee(s) who have taken more active part in any subanalysis and thus fulfil the Vancouver criteria for authorship must be included by name in the list of authors. All other members must be individually named in Acknowledgements. The Coordinating Investigator must be co-author in any publication using data from the SENOMAC trial.

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