
# INSPIRE

## INTERNATIONAL NIPPLE SPARING MASTECTOMY REGISTRY

## an EURECCA project

**Riccardo A. Audisio and Isabel T. Rubio**
**Principal Investigators**

# TABLE OF CONTENTS

## 1. BACKGROUND

Nipple Sparing Mastectomy (NSM) entails the conservation of the nipple–areola complex (NAC) as well as the skin envelope while performing a complete excision of all the mammary gland; NSM is a recently introduced alternative to modified radical, total and skin sparing mastectomy where the NAC is removed and it is also different from subcutaneous mastectomy. NSM and immediate breast reconstruction has been practiced more and more often in the last decade in treating invasive breast cancer as well as precancerous conditions such as DCIS and for women with an increased risk of developing breast cancer.

One significant advantage of the NSM technique is the removal of the whole breast tissue as a radical surgical procedure while preserving native breast integrity, the nipple-areola complex as well as the submammary fold, therefore improving the cosmetic outcomes.

Several recently reports seem to suggest that the oncologic outcomes of NSM are comparable to a skin-sparing mastectomy, with locoregional recurrence rates as low as 2 % at 3-year follow-up. As NSM techniques have evolved over time, complications have been reduced to acceptably low rates, making the approach technically feasible and safe. Furthermore, excellent aesthetic outcomes and high levels of patient satisfaction after reconstruction have been achieved; this is particularly important for women considering bilateral mastectomy for the purpose of reducing the risk of developing a breast cancer.

As rates of NSM continue to increase, it is important to retrieve confirmatory evidence in support of the oncologic safety of the technique for therapeutic as well as risk reducing indications in high-risk patients. Women, whether affected by breast cancer or exposed to an increased risk, deserve full information on the advantages and drawbacks of NSM, as derived from solid investigations.

## 2. RATIONALE

Modified radical mastectomy and simple mastectomy routinely remove the NAC mostly due to a concern of its possible involvement by malignant cells and the hypothetical increased risk of developing local recurrences with consequent poor cosmetic results. In the last decade,

several studies have shown that NAC involvement is not as high as it was thought from historical evidence and more knowledge about the NAC anatomy and the terminal ductal lobular unit in the nipple has spread its practice. Nipple sparing techniques with immediate breast reconstruction may increase the patient´s satisfaction and improve the body image; this may result into psychological benefits for the patients facilitating the recovery process of the breast cancer diagnosis.

However, there is a lack of robust evidence for the routine use of NSM. A prospective, consecutive and standardized registration will pool patients' data together, in order to overcome any selection bias or limited sample size.

There is a need for this international registry because:

1. New surgical techniques need to be proven feasible, safe and validated before implementation. A well designed prospective database is required to reduce uncertainty regarding NSM;

2. At present, a randomized clinical trial for nipple sparing techniques vs. conventional mastectomy (followed by reconstruction) is neither feasible nor ethical;

3. NSM is only performed by a limited number of breast units, therefore most patients and physicians are not fully informed about this alternative to a traditional mastectomy and reconstruction;

4. No standardized staging, surgical technique or surveillance protocol for NSM is presently available;

5. There is a need for a network of interested clinicians to optimize NSM techniques in an evidence based way to identify and promote best patterns of care.

## 3. EURECCA NSM REGISTRY PURPOSES

The INSPIRE project aims to gain insight in treatment strategies for women undergoing NSM and immediate breast reconstruction for breast cancer or for risk reducing purposes. The target is to provide a prospective robust evidence on its oncological safety, complications

(associated risks of nipple and skin necrosis, infection rates, reconstruction loss, nipple symmetry) and patient reported outcome measures (PROMs).

The INSPIRE project will provide pooled evidence derived from a prospective collaborative high-quality registry between international centers to implement NSM. These findings will clarify if and how NSM can safely become part of our daily armamentarium.

Primary objectives are:

1. To determine oncological safety of NSM

Secondary Objectives:

2. To investigate NSM's outcomes, complications rate from surgery and radiation therapy
3. To compare details relevant to surgical techniques and preoperative imaging
4. To obtain evidence-based information which will assist in the treatment planning of future patients who are offered a mastectomy for cancer treatment or as a risk-reducing procedure
5. To assess patient´s satisfaction (quality of life questionnaire)

INSPIRE network rests on the agreement that; 1) each center owns its own data; 2) there will be no data sharing with any third party; 3) personal data will be anonymised and confidential encrypted in a secure place; 4) professional support for (big) data analysis will be made available; 5) results will be published collaboratively.

# 4. PROTOCOL

## 4.1 Centers and Investigators

Participating investigators will be surgeons/gynecologist/plastic surgeons whose practice is based at an Institution with a Breast Cancer Program. These centers have experience in breast cancer treatment and offer NSM as a surgical option for their patients in a routinely basis.

Each participating investigator will require approval from the Institutional review board and/or the Ethics Committee before contributing cases into the Registry.

Participant investigators will obtain a written informed consent from each patient eligible for NSM, ahead of surgery. They will provide accurate data, take digital pictures and commit to send follow up data of these patients during the follow-up 5- year period.

Annual evaluation of patient data entry, activity of the participation centers, and cohesion of the centers will be shared and published by the group of collaborators. Interim findings will be presented at scientific conferences to ensure visibility of the generated results.

### 4.2 Design

INSPIRE is a non- randomized prospective observational multicenter cohort study (Phase IV “real life” trial).

Recruiting centers will enter data prospectively. The original treatment plan, as designed by each individual recruiting centre, will not be altered or affected.

Recruited patients will be followed for 5 years.

### 4.3 Study population

*Inclusion*

- Female patients 18 years and older
- Intention to undergo a NSM with immediate reconstruction
- Stratified in two distinct groups (two parallel studies):
    - DCIS or invasive breast cancer
    - Risk reducing mastectomy

*Exclusion*

All consecutive patients who undergo NSM are eligible for inclusion into this prospective database. Selection for NSM is at the physicians’ discretion.

### 4.4 Research questions and endpoints

| **DCIS / Invasive breast cancer** | **Risk reducing** |
|---|---|
| Research questions | |
| 1. Determine the oncological outcome of NSM in terms of local control<br>2. Determine the occurrence of distant metastases rate and survival (breast cancer specific survival and overall survival)<br>3. Determine the complication rate of NSM<br>4. Assess aesthetic outcomes and patient satisfaction<br>5. Compare surgical techniques | 1. Determine the oncological outcome of NSM (breast cancer occurrence)<br>2. Determine the complication rate of NSM in patients with risk reducing mastectomy<br>3. Assess aesthetic outcomes and patient satisfaction<br>4. Compare surgical techniques |
| Primary endpoint | |
| Local recurrence rate/disease free survival | Breast cancer incidence at 5 years |
| Secondary endpoints | |
| Overall survival<br>Complication rate (i.e. infection, necrosis, etc)<br>Cosmetic Outcome (assessed by the patient and physician)<br>Surgical techniques | Complication rate (define in the data sheet)<br>Cosmetic Outcome (assessed by the patient and physician)<br>Surgical techniques |

### 4.5 Registry Material

The study protocol will be assessed and approved by the local ethical committee or Hospital audit/research/governance committee. The protocol will be supplied to all interested investigators. The following forms will be filled in for each recruiting centre and each recruited patient:

- Investigator Agreement to participate in the study **(Attached A)**
- Patient Permission **(Attached B)**

### 4.6 Sample size calculation

*DCIS / Invasive breast cancer*

The study is designed as a non-inferiority study with respect to the patients with DCIS or invasive breast cancer with the aim to demonstrate that NSM is not inferior in local control to standard treatment (mastectomy).

The sample size calculation is performed for patients with DCIS and/or invasive breast cancer. The local recurrence rate after mastectomy is approximately 4% at 5 years and the non-inferiority limit is set at 2% for NSM; with an alpha of 0.05 and power 80, 530 patients are required to be 80% sure that the upper limit will exclude a difference of more than 2%.

*Risk reducing mastectomy*

For patients who receive a risk reducing mastectomy, we expect the breast cancer incidence to be negligibly low. No sample size calculation is performed for this part of the study; all consecutive patients who underwent a risk-reducing NSM will be included. and the complication rate will be yearly reviewed.

## 5. DATA COLLECTION

An International Quality Registry will secure standardized collection of data from all patients undergoing NSM from participating centers. To avoid a selection bias, patients will prospectively be entered into the registry after signing the informed consent. Pre-operative photographic documentation will be produced as well as follow-up pictures during outpatient clinics.

Recruiting centers are fully responsible for accurate data entry; the datacenter will be able to act upon data entry with queries by sampling.

*ACCESS, MAINTENANCE, OWNERSHIP AND LOCATION OF DATA*

1. Per research question, the INSPIRE executive board will determine a principal investigator and support staff, who will be responsible for the analyses and data management. She/he will also share the results of the analyses with the rest of the participants. Authorship is guaranteed when active input is delivered (minimum 10 patients with full data collection). This will be discussed per project and need to be approved by the participants and the INSPIRE executive board.
2. Participants shall retain the ownership of their own data. Each participating centre is responsible for accurate data entry and has access to their data only.
3. Data collected for specific research questions will be analyzed coded and is stored de-identified. Data are stored in a highly secured and encrypted research data server:

   
   

   Advanced Data Management (ADM), based in Leiden University Medical Center, Leiden, The Netherlands, is NEN7510 certified and ProMISe meets the requirements for data-safety and privacy set by international law. Due to this certification the ProMISe system facilitates the availability, integrity and confidentiality of your data. ProMISe facilitates you to store, exchange and retrieve data according to the security conditions demanded by GCP.
4. An additional local stored database can be added for i.e. imaging data. Local investigators carry responsibility for this.
5. Name of the ProMISe database: INSPIRE
6. Multicenter, every center has a unique number between 1001 and 2000
7. Username is combination of project name, center number and initials

8. Password: ask at logon for new password. Security code sent to email. Every investigator has its own username (logfile)
9. www.clinicalresearch.nl/PROMISE/S/HEIT/S_O_LUMC_C_HEELK_**INSPIRE**_/LOGON/INDEX.HEI

Access to the data will be only available to the researchers involved in the INSPIRE Project and the working staff. All participating units will be acknowledged for their participation and patients accrual; the Unit will be acknowledged on scientific publications and presentations.

## 6. RISKS and BENEFITS

The participation into this registry does not involve any risks for the patient. Access to patient´s information will be restricted to the investigators and designated staff. Patient identity will not be revealed at any point.

There is no direct benefit from the study although patients will be accurately monitored and best standards of care will be promoted. Future patients will take advantage from the results generated by INSPIRE in terms of the improved knowledge regarding the validity of this procedure.

All patients undergoing NSM, for treatment of their breast cancer or as a risk reducing purposes will be prospectively followed and their outcomes will be closely monitored in order to ensure that best practice is identified and promoted.

## 7. STATISTISCAL ANALYSIS

Statistical analysis will be performed using SPSS including all the parameters within the Registry. Analysis will include logistic regression, Cox proportional hazard regression and survival analysis.

After data cleaning with specific attention for identical definitions for variables, the dataset will be split in two parts. For cancer patients, the local recurrence rate will be calculated using KM survival curves. Time from diagnosis to recurrence or end of follow-up will be used as time and any local recurrence as event. For the secondary endpoint Overall Survival, KM survival curves will be used with death due to any cause as event and the same time from diagnosis to death or end of follow-up. Complications will be recorded and the complication rate will be calculated for specific subgroups of complications. Cosmetic outcome will be assessed by the patient and physicians using questionnaires and the results will be reported in proportions. Surgical techniques will be compared using chi-square test or multivariable logistic regression where appropriate. For the risk reducing group, breast cancer incidence at 5 years will be calculated. The secondary endpoints will be studied as described above. Where appropriate multivariable models will be used, adjusting for potential confounders. Model fit will be tested as well as possible interaction terms in the model. When statistical interaction is found, stratified analyses will be performed.

## 8. REFERENCES


Rusby JE et al. Microscopic anatomy within the nipple: implications for nipple-sparing mastectomy. The American Journal of Surgery 2007; 194: 433-437.

Hartmann LC, Sellers TA, Schald DJ,. et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 2001; 93 (21): 1633-7

Rusby JE, Brachtel EF, Othus M et al. Development and validation of a model predictive of occult nipple involvement in women undergoing mastectomy. British Journal of Surgery 2008; 95:1351-1361.

Stolier AJ, Levine EA. Reducing the risk of nipple necrosis: technical observations in 340 nipple-sparing mastectomies. Breast J. 2013;19:173–9.

Loewen MJ, Jenning JA, Sherman SR, et al. Mammographic distance as a predictor of nipple-areola complex involvement in breast cancer. The American Journal of Surgery 2008; 195: 391-395.

Peled AW, Foster RD, Stover AC, et al. Outcomes after total skin-sparing mastectomy and immediate reconstruction in 657 breasts. Ann Surg Oncol. 2012; 19:3402–9.

Gerber B. et al. The Oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg 2009;249(3):461-4

Garcia-Etienne CA, Cody III HS, et al. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. Breast J. 2009; 15:440–9.

Munhoz AM, Aldrighi CM, Montag E, et al. Clinical outcomes following nipple-areola-sparing mastectomy with immediate implant-based breast reconstruction: a 12-year experience with an analysis of patient and breast-related factors for complications. Breast Cancer Res Treat. 2013 Aug;140(3): 545-55.

Denewer A. Farouk O. Can nipple-sparing mastectomy and immediate breast reconstruction with modified wxtended latissimus dorsi muscular flap improve the cosmetic and functional outcome among patients with breast carcinoma? World J Surg 2007; 31:1169-1177

Kneubil MC, Lohsiriwat V, CuriglianoG et al. Risk of locoregional recurrence in patients with false-negative frozen section or close margins of retroareolar specimen in nipple-sparing mastectomy. Ann Surg Oncol. 2012 Dec;19(13):4117-23.

Reynolds C, Davidson J, Lindor NM, et al. Prophylactic and therapeutic mastectomy in BRCA mutation carriers: Can the nipple be preserved? Ann Surg Oncol 2011; 18: 3102-3109

Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, Koerner FC. Occult nipple involvement in breast cancer: clinicopathologic findings in 316 consecutive mastectomy specimens. Journal of Clinical Oncology 2009; 27:4948-4954.

Petit JY, Veronesi U, Orecchia R et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five year experience at the European Institute of oncology of Milan (EIO). Breast Cancer Res Treat 2009;117(2):333-8

Piper M, Peled AW, Foster RD, Moore DH, Esserman LJ. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. Ann Plast Surg. 2013;70:435–7.

Algaithy ZK, Petit JY, et al. Nipple-sparing mastectomy: can we predict the factors predisposing to necrosis? Eur J Surg Oncol. 2012;38:125–9.

Pusic AL, Klassen AF, Scott AM et al. Development of a new patient reported outcome measure for breast surgery. The Breast Q. Plast Reconstr Surg 2009; 124: 345-353

Temple-Oberle CF, Cook EF, Bettger-Hahn M, et al. Development of a breast reconstruction satisfaction questionnaire (BRECON-31): principal components analysis and clinimetric properties. J Surg Oncol. 2012 Dec;106(7):799-806.

Rusby JE, Smith BL, Gui GPH. Nipple Sparing Mastectomy. British Journal of Surgery 2010;97:305-316.

De La Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM. Overall survival, disease free survival, local recurrence and nipple-areolar recurrence in the setting of nipple sparing mastectomy: a meta-analysis and systematic review. Ann Surg Oncol. 2015 Aug 5. [Epub ahead of print

Didier F, Radice D, Gandini S, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image, and sexuality? Breast Cancer Res Treat 2009;118(3): 623-33.

Yueh J H. Houlihan MJ, Slavin SA, et al. Nipple-Sparing Mastectomy. Evaluation of Patient Satisfaction, Aesthetic Results,and Sensation. Annals of Plastic Surgery 2009; (62)5; 586-590.

Mutter RW, Frost MH, Hoskin TL, et al. Breast cancer after prophylactic mastectomy. A clinical entity: presentation, management and outcomes.Breast Cancer Res Treat. 2015;153(1):183-90