Ann Surg Oncol (2019) 26:1254–1262
https://doi.org/10.1245/s10434-019-07259-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Prospective Evaluation of Residual Breast Tissue After Skin- or Nipple-Sparing Mastectomy: Results of the SKINI-Trial

Bärbel Papassotiropoulos, MD[1], Uwe Güth, MD[2], Federica Chiesa, MD[2], Christoph Rageth, MD[2], Esther Amann, MD[2], Astrid Baege, MD[2], Constanze Elfgen, MD[2], Zsuzsanna Varga, MD[3], Linda Moskovszky, MD[3], Katharina Endhardt, MD[3], Regina Masser, MD[4], Marianne Tinguely, MD[4], Jian Farhadi, MD[5], Alessia Lardi, MD[5], Florian Dammann, MD[6], Joachim Diebold, MD[7], Qiyu Li, MSc[8], Peter Dubsky, MD[9,10], and Christoph Tausch, MD[2]

[1]Clinical Trial Unit, Brust-Zentrum, Zurich, Switzerland; [2]Department of Breast Surgery, Brust-Zentrum, Zurich, Switzerland; [3]Institute of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland; [4]Pathologie Institut Enge, Zurich, Switzerland; [5]Department of Plastic Surgery, Brust-Zentrum, Zurich, Switzerland; [6]Radiology, Brust-Zentrum, Zurich, Switzerland; [7]Pathology, Lucerne Cantonal Hospital, Lucerne, Switzerland; [8]Statistician Unit, Swiss Group for Clinical Cancer Research, Bern, Switzerland; [9]Breast Center, Hirslanden Clinic St. Anna, Lucerne, Switzerland; [10]Department of Surgery, Medical University of Vienna, Vienna, Austria

Objective. This study was designed to investigate the presence of residual breast tissue (RBT) after skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) and to analyse patient- and therapy-related factors associated with RBT. Skin-sparing mastectomy and NSM are increasingly used surgical procedures. Prospective data on the completeness of breast tissue resection is lacking. However, such data are crucial for assessing oncologic safety of risk-reducing and curative mastectomies.

Methods. Between April 2016 and August 2017, 99 SSM and 61 NSM were performed according to the SKINI-trial protocol, under either curative (n = 109) or risk-reducing (n = 51) indication. After breast removal, biopsies from the skin envelope (10 biopsies per SSM, 14 biopsies per NSM) were taken in predefined radial localizations and assessed histologically for the presence of RBT and of residual disease.

Results. Residual breast tissue was detected in 82 (51.3%) mastectomies. The median RBT percentage per breast was 7.1%. Of all factors considered, only type of surgery (40.4% for SSM vs. 68.9% for NSM; $P < 0.001$) and surgeon ($P < 0.001$) were significantly associated with RBT. None of the remaining factors, e.g., skin flap necrosis, was associated significantly with RBT. Residual disease was detected in three biopsies.

Conclusions. Residual breast tissue is commonly observed after SSM and NSM. In contrast, invasive or in situ carcinomas are rarely found in the skin envelope. Radicality of mastectomy in this trial is not associated with increased incidence of skin flap necrosis.

ClinicalTrials.gov Identifier NCT03470909.

The frequency of skin-sparing and nipple-sparing mastectomies (SSM and NSM, respectively) has increased significantly over the past years due to a number of reasons. For example, growing awareness of familial and genetic factors predisposing to breast cancer has led to a higher number of risk-reducing mastectomies.[1] In addition, continuously improved diagnostic procedures increase the detection rate of widespread ductal carcinoma in situ (DCIS) components and multicentric tumors that do not require conventional mastectomy. Skin-sparing mastectomy and NSM are meanwhile considered as established and safe surgical procedures with superior cosmetic

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07259-1) contains supplementary material, which is available to authorized users.

First Received: 6 January 2019;
Published Online: 4 March 2019

B. Papassotiropoulos, MD
e-mail: b.papassotiropoulos@brust-zentrum.ch

outcome compared with conventional mastectomies.[2–6] While SSM was already introduced in 1991, NSM has been being performed since 2001.[7–11]

Both mastectomy techniques were designed to remove the entire breast tissue under concomitant preservation of the skin envelope and the inframammary fold, thereby enabling immediate breast reconstruction. Because the breast maintains its natural shape and contour, cosmetic results surpass the results of conventional mastectomies. Several retrospective and some prospective studies reported a satisfying oncological outcome regarding local recurrence after SSM and NSM, which is comparable to the outcome of conventional mastectomy, and even NSM without consecutive radiotherapy has been shown to be safe.[2,3,12–22]

Superior cosmetic results, increasing surgical experience and promising safety data, suggest that the frequency of SSM and NSM will increase. However, the surgical challenge of removing a maximum amount of breast tissue while achieving low morbidity and the best possible cosmetic result via an adequate skin envelope will remain. Both in oncological and risk-reducing surgery, residual breast tissue (RBT) can be considered as a potential risk factor for breast cancer recurrence or increased breast cancer incidence, respectively.

Thus, there is a need to investigate prospectively the radicality of SSM and NSM with regard to the amount of histologically detected RBT or residual disease under the skin envelope. To our knowledge, three trials using three different methods investigated hitherto the radicality of SSM, yielding conflicting results. In 42 patients, Torresan et al. performed a modified SSM and removed the skin flap for subsequent assessment of RBT and residual disease. In this study, RBT was reported in 60% and residual disease in 10% of the mastectomies.[23] Dreadin et al. investigated skin specimens that were removed during SSM for nononcological reasons and immediate reconstruction in 66 patients. They reported RBT in 6% of mastectomies but no residual disease.[24] Slavin et al. assessed 114 biopsies taken from the remaining native skin flap edges after periareolar SSM in 32 patients and reported no RBT.[25] In a related study, Reynolds et al. evaluated the prophylactic and therapeutic value of NSM and examined histologically for RBT and residual disease a total of 62 excised nipple-areolar-complexes (NAC) from 33 BRCA mutation carriers. They found RBT within the NAC in 24% of all cases and residual disease in 3% of the 29 therapeutic cases.[26] In the present prospective trial, we assessed the radicality of SSM and NSM by quantifying the presence of RBT and of residual disease. Importantly, we assessed patient- and therapy-related factors that might be associated with RBT and evaluated the surface of the mastectomy specimens with respect to the distance to the breast tissue.

METHODS

Before mastectomy, each patient was informed about the study scope and design and gave written, informed consent. The research protocol (KEK-ZH-Nr. 2015-0565) was approved by the local ethics committee of the Canton of Zurich, according to the national and international ethics guidelines. Mastectomies were performed at the Brust-Zentrum Zürich (n = 152) and the Brust-Zentrum St. Anna Hospital in Lucerne (n = 8). Only surgeons with high surgical volumes (i.e., at least 50 surgeries per year) participated in the trial.

In cases of curative indication, the decision to perform SSM or NSM was primarily based on tumor characteristics, such as tumor size, tumor location, and DCIS-component, and on patient characteristics, such as breast shape, breast size, and previous surgery. Patients‘ preference also was considered whenever it did not contradict the medical indication. NSM was the standard procedure in cases of risk-reducing indication.

To assess the presence of RBT after SSM and NSM, biopsies were taken from the remaining skin envelope immediately after breast removal. The biopsy procedure was performed according to a predefined pattern of radial localizations: 10 biopsies per SSM, and 14 biopsies per NSM. Thus, in the case of NSM four additional biopsies were taken under the peripheral part of the areola (Fig. 1). A mastectomy was defined as RBT-positive whenever RBT was detected in one or more biopsies.

Five additional incisions (A_2–E_2) were marked on the excised mastectomy specimens. Their localization corresponded to biopsy points A–E of the skin envelope. Pathologists were instructed to measure the distance between specimen surface and glandular tissue at these marked incision points (Fig. 2, points A_2–E_2). Low distance was defined as < 1 mm in each of the points A_2–E_2, large distance was defined as ≥ 1 mm in at least one of the points A_2–E_2.

Participating pathology institutes are qualified partners of the certified breast centres. Involved pathologists were trained on the study-specific assessment procedures. Surgeons remained blinded to the pathology results of the biopsies and to the surface distances until the end of the trial. Blinding was lifted whenever tumour tissue was detected in the biopsies. In these cases, surgeons and patients were informed and further therapeutic steps were decided upon at a multidisciplinary postoperative tumour board. The number of mastectomies per surgeon ranged between 6 and 65 (3.8% and 40.6% of all mastectomies, respectively).

Patient- and therapy-related data were collected to assess the relation of RBT to such factors as age, side, body mass index, indication for surgery, kind of axillary surgery,

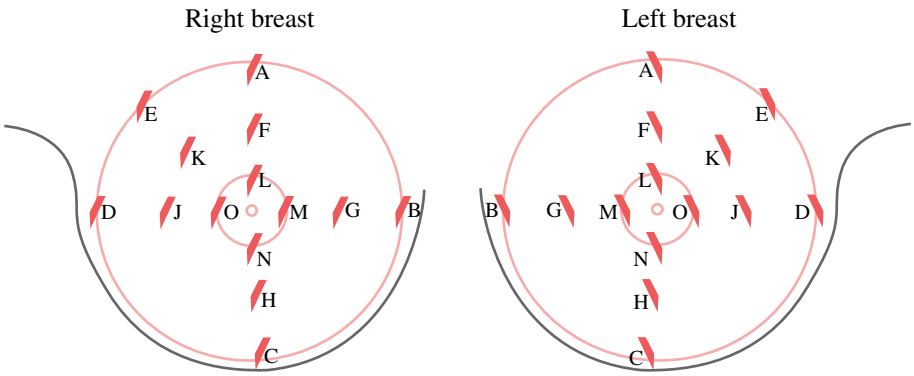

FIG. 1 Pattern of biopsy points in SSM (A–K) and NSM (A–O)

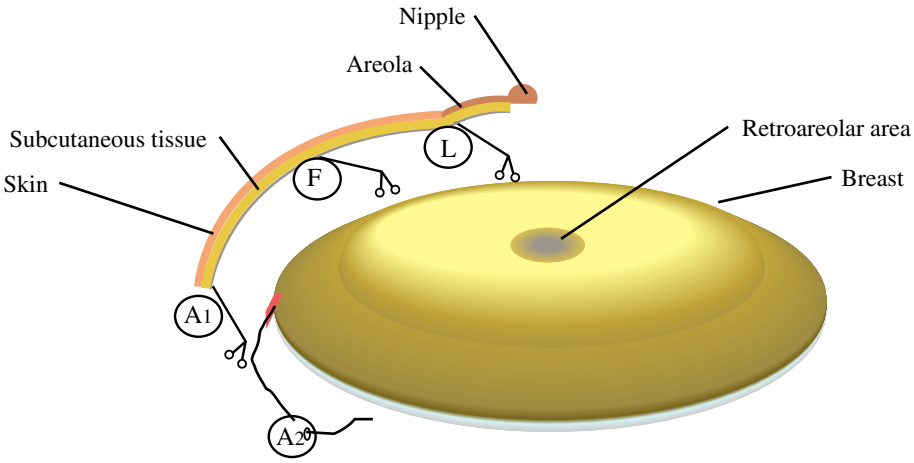

FIG. 2 Anatomical visualization of biopsy points in SSM and NSM in 12 o'clock position (A1, F, L) and incision points on the removed specimen in opposite (A2)

breast weight, surgeon, type of surgery, type of incision, as well as evidence and severity of mastectomy skin flap necrosis due to perfusion disorders (as defined by the SKIN Score).[27] Evidence for and severity of mastectomy skin flap necrosis was assessed with the SKIN Score, which was determined by the plastic surgeon during the postoperative assessment.[27] The SKIN Score system incorporates both depth and surface area of skin flap necrosis. "No necrosis" is defined as SKIN Score A1 (whereby "A" stands for no evidence for necrosis regarding depth and "1" stands for no evidence for necrosis regarding surface area). Anything beyond A1 (e.g., B1 or A2) is defined as evidence for necrosis.

Statistics

Statistical analyses were performed with the Statistical Package for the Social Sciences (IBM® SPSS® Statistics, Version 21, IBM Corp., Armonk, NY). Comparisons of patient- and therapy-related variables between SSM and NSM were done with χ^2 and Student's t tests for equal or unequal variances, wherever applicable. Logistic regression was used to assess the influence of putative risk factors on RBT, which served as binary dependent variable (0: no RBT; 1: at least one probe with positive breast tissue detection). Age, BMI, and breast weight served as continuous independent variables. Side of mastectomy (left vs. right), type of mastectomy (SSM vs. NSM), and skin flap necrosis (no necrosis vs. evidence for necrosis) served as binary independent variables. Indication for mastectomy, axilla surgery, preoperative treatment, surgeon, and incision type served as categorical independent variables (simple contrast scheme used). Results presented herein correspond to the final, concordant solution of the forward and backward selection. At each step, variables were included at nominal $P < 0.05$ and excluded at $P > 0.1$. For all tests, the level of significance was 0.05.

RESULTS

Between April 2016 and August 2017, 124 patients with an indication for SSM or NSM were included in the trial. Thirty-six of these patients underwent bilateral mastectomy, resulting in 160 mastectomies (99 SSM, 61 NSM) in total (Table 1). The mastectomies were performed by seven surgeons. Indications for mastectomy were either risk-reducing ($n = 51$) or curative for histologically confirmed invasive ($n = 83$) or in situ breast cancer ($n = 26$).

Patients receiving NSM were significantly younger than patients receiving SSM (SSM: 51.6 ± 11.2 years; NSM: 46.1 ± 11.1 years, $P = 0.011$). BMI was significantly lower in patients who received NSM ($P = 0.001$; Table 1). Fifteen of 99 SSMs (15.1%) and 36 of 61 NSMs (59%) were performed for risk-reducing reasons.

Residual Breast Tissue Detection

Residual breast tissue was detected in 82 (51.3%) of 160 mastectomies. The median RBT percentage per breast was 7.1%. RBT-positive biopsies were homogeneously distributed between peripheral points A–K (3–11%) and were found in significantly more cases in the central biopsy sites L-0 behind the areola (18–28%, $P < 0.001$, Person's χ^2 test; Fig. 3). Residual tumour tissue was detected in one SSM (point F) and in one NSM (points M and N), which corresponds to 0.25% of 1,190 biopsies that were taken from curative mastectomies. Reexcision was performed in both cases.

Residual Breast Tissue-Associated Factors

In the logistic regression, only the factors type of surgery, i.e., NSM vs. SSM, and surgeon contributed significantly to RBT ($P < 0.001$ for both variables; Table 2). The proportion of RBT in NSM was significantly higher than in SSM (68.9% vs. 40.4%, $P < 0.001$). Further analysis of the factor surgeon revealed that surgeon #1, who performed most mastectomies ($n = 65$), had a significantly lower rate of RBT (26.2%, $P < 0.001$) compared with the other surgeons. The number of mastectomies per surgeon was highly variable and ranged between 6 and 65 mastectomies. All surgeons performed SSMs (ranging between 4 and 33 mastectomies per surgeon) as well as NSMs (ranging between 1 and 32 mastectomies per surgeon) (Supplemental Table 1). Between-surgeon RBT rate ranged between 26.2% and 100%. However, the latter result (100% RBT rate) should be taken with caution because of the low overall number of mastectomies ($n = 8$) of the particular surgeon (Supplemental Fig. 1).

With the exception of indication for mastectomy, categorical independent variables (i.e., axilla surgery, preoperative treatment, surgeon, and incision type) contained a relatively high number of low-frequency (≤ 5%; Table 1) subcategories. To test the stability of the logistic regression, we re-ran the analysis by using a binary coding scheme for the respective variables (i.e., no axilla surgery vs. rest, no preoperative treatment vs. rest, surgeon #1 vs. rest, periareolar incision vs. rest). As in the first analysis, only the factors type of surgery (i.e., NSM vs. SSM) and surgeon (i.e., surgeon #1 vs. rest) contributed significantly to RBT ($P < 0.001$ for both variables). Because two of the included factors (i.e., age and BMI) were patient- rather than mastectomy-specific, we repeated the analysis by considering only a subset of 124 mastectomies (i.e., 1 mastectomy per patient). In the case of patients undergoing bilateral surgery, the respective mastectomy was selected randomly. Again, only the factors type of surgery and surgeon contributed significantly to RBT ($P < 0.001$ and $P = 0.005$, respectively).

Skin Flap Necrosis

Skin flap necrosis was not related to the presence of RBT ($P = 0.207$; Table 2). Of the additional patient- and therapy-related factors, only type of surgery had a borderline significant influence on the incidence of skin flap necrosis, with higher incidence detectable when the nipple was preserved (mastectomies with detectable skin flap necrosis: 17/61 NSM vs. 15/99 SSM, $P = 0.051$).

Distance Between Tissue and Specimen Surface

In an additional step, pathologists assessed the distance between breast glandular tissue and the circumferential/anterior surface of the removed specimen at five defined points (Fig. 2). Distances ranged between 0 mm to > 10 mm with a high between-point variability. Left breast side, high BMI, and RBT in points A–K were significantly associated with lower distance between specimen surface and breast glandular tissue (linear regression, $P = 0.004$, $P = 0.003$, and $P = 0.045$, respectively). Conversely, an increased distance between breast tissue and circumferential/anterior surface of the mastectomy specimen correlated with low RBT rate (Supplemental Fig. 2).

DISCUSSION

We detected at least one RBT-positive biopsy in 51.3% of the mastectomies in the present study. Previous trials examining the rate of histologically detected RBT after SSM or NSM reported RBT rates ranging between 0% and 60%.[23–26] This high variability is probably caused by the different methods used to assess RBT. For example,

TABLE 1 Patients and mastectomy characteristics

	SSM (n = 99)	NSM (n = 61)	P	Total (n = 160)
No. of patients with unilateral mastectomy	66	22	–	88
No. of patients with bilateral mastectomy[a]	17	20	–	36
No. of RBT-positive mastectomies[b]	40 (40.4%)	42 (68.9%)	< 0.001	82 (51.3%)
Age (yr)[c]				
Mean (SD)	51.6 (11.2)	46.1 (11.1)	0.011	49.8 (11.4)
(95% confidence interval)	(49.2–54.1)	(42.6–49.7)		
Body Mass Index (kg/m^2)[c]				
Mean (SD)	23.3 (3.5)	21.5 (2.4)	0.001	22.8 (3.3)
(95% confidence interval)	(22.6–24.1)	(20.8–22.3)		
Breast weight (g)				
Mean (SD)	366 (195)	319 (126)	0.067	348 (174)
(95% confidence interval)	(332–400)	(276–363)		
Indication for mastectomy				
Curative (preinvasive carcinoma)	18 (18.2%)	8 (13.1%)	< 0.001	26 (16.2%)
Curative (invasive carcinoma)	66 (66.7%)	17 (27.9%)		83 (51.9%)
Risk-reducing	15 (15.1%)	36 (59.0%)		51 (31.9%)
Axilla surgery				
No axilla surgery	14 (14.1%)	31 (50.8%)	< 0.001	45 (28.1%)
Simultaneous sentinel node biopsy	56 (56.6%)	17 (27.9%)		73 (45.6%)
Simultaneous axillary dissection	17 (17.2%)	5 (8.2%)		22 (13.7%)
Previous sentinel node biopsy	8 (8.1%)	6 (9.8%)		14 (8.8%)
Previous axillary dissection	4 (4.0%)	2 (3.3%)		6 (3.8%)
Side of mastectomy				
Left	50 (50.5%)	29 (47.5%)	0.716	79 (49.4%)
Right	49 (49.5%)	32 (52.5%)		81 (50.6%)
Preoperative treatment				
No preoperative treatment	67 (67.7%)	38 (62.3%)	0.874	105 (65.6%)
Chemotherapy (CT)	7 (7.1%)	6 (9.8%)		13 (8.1%)
Breast-conserving surgery (BCS)	20 (20.2%)	13 (21.3%)		33 (20.6%)
Both (CT + BCS)	5 (5.0%)	4 (6.6%)		9 (5.6%)
No. of mastectomies per surgeon				
Surgeon #1	33 (33.3%)	32 (52.4%)	0.114	65 (40.6%)
Surgeon #2	15 (15.2%)	3 (4.9%)		18 (11.2%)
Surgeon #3	26 (26.3%)	15 (24.6%)		41 (25.6%)
Surgeon #4	7 (7.1%)	1 (1.6%)		8 (5.0%)
Surgeon #5	10 (10.1%)	4 (6.6%)		14 (8.8%)
Surgeon #6	4 (4.0%)	2 (3.3%)		6 (3.8%)
Surgeon #7	4 (4.0%)	4 (6.6%)		8 (5.0%)
Incision type				
Periareolar	91 (92.0%)	4 (6.6%)	< 0.001	95 (59.4%)
Submammary fold	0 (0.0%)	31 (50.8%)		31 (19.4%)
6 o'clock	0 (0.0%)	7 (11.5%)		7 (4.4%)
Radial (upper outer quadrant)	1 (1.0%)	11 (18.0%)		12 (7.5%)
Mixed (periareolar radial)	4 (4.0%)	1 (1.6%)		5 (3.1%)
Other	3 (3.0%)	7 (11.5%)		10 (6.2%)
Skin flap necrosis				
No	84 (84.8%)	44 (72.1%)	0.051	128 (80.0%)
Yes	15 (15.2%)	17 (27.9%)		32 (20.0%)

SD standard deviation

[a]One patient underwent SSM and NSM

[b]One or more RBT-positive biopsies per mastectomy

[c]These variables are patient-specific. Statistical comparisons between SSM and NSM refer to 83 patients undergoing SSM and 41 patients undergoing NSM. For the purposes of this table, one patient who underwent both SSM and NSM was assigned to the SSM group

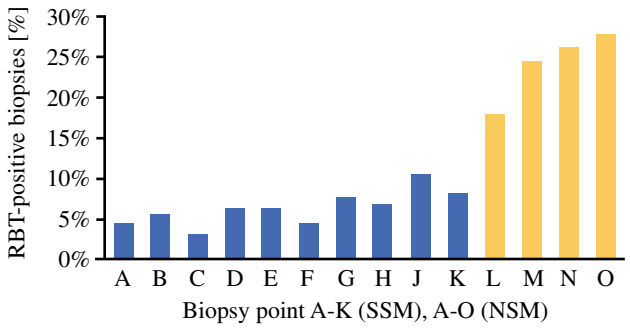

FIG. 3 Incidence of RBT in different biopsy points

Torresan et al. performed a modified SSM and removed the skin flap for subsequent assessment of RBT and residual disease. While the number of patients was low (n = 42), a large number (n = 80) of glass slides per skin flap was examined under an optical microscope. The authors reported RBT in 60% and residual disease in 10% of the cases.[23] However, these results cannot be easily translated to the actual SSM situation, because the examined skin flaps were removed. In another study, Slavin et al. took 114 biopsies from the remaining native skin flap edges after periareolar SSM in 32 patients and reported no RBT. However, the number of biopsies per mastectomy varied from one to four, and biopsies were taken only at the edges of the skin flap and not at other points under the skin.[25] Therefore, it is questionable whether the results of this study are generalizable.

Few additional attempts to measure RBT after SSM and NSM do exist, albeit each following a different methodology.[24,26] The rather limited number of attempts to measure RBT so far along with the considerable variation in methodology renders the assessment of RBT after SSM and NSM challenging. Nevertheless, there is a need for reliable data on the presence of RBT and remaining tumour tissue after SSM and NSM with regard to oncologic safety of risk-reducing and curative mastectomies.

In our trial, we used a sensitive method with a higher number of mastectomies (n = 160) and biopsies (n = 1,844) to obtain representative and robustly quantifiable results. Moreover, our study adopted a prospective design, as biopsies were taken under the remaining skin envelope during routinely performed SSM or NSM. Importantly, biopsies were taken using a predefined scheme in each of the 160 mastectomies throughout the whole skin envelope after breast removal, resulting in a total of 1,844 biopsies.

Based on the high number of biopsies (n = 1,844) and the standardized biopsy scheme, we used the median RBT percentage per breast (7.1%) as an approximation of RBT-positivity in the 160 mastectomies. We acknowledge that this approximation might be limited given that not the entire area under the skin envelope was tested. However, an even denser pattern of biopsies to reach a more accurate conclusion would not have been feasible. The low percentage of residual tumour tissue (i.e., 3 of 1,190 biopsies taken from 109 curative mastectomies) confirms the efficacy of SSMs and NSMs regarding complete resection of invasive and in situ lesions.

We would like to stress that our study focused on factors influencing RBT detection specifically after SSM and NSM, because these techniques represent the vast majority of mastectomies performed in the participating centres. Thus, a comparison with conventional mastectomy is not provided.

With regard to patient- and therapy-related factors possibly influencing the occurrence of RBT, the assumption that high breast weight or BMI is linked to increased RBT was not confirmed. This also was the case for the factors age, indication of surgery, and type of incision. We note that type of incision was tightly linked to type of mastectomy. For example, a periareolar incision was almost exclusively used in SSM. Both factors entered the stepwise logistic regression model, which revealed that type of mastectomy was strongly associated with RBT. No additional variance regarding RBT was explained by the factor incision type.

Unlike Dreadin et al., we observed that the factor surgeon contributed highly significantly to the percentage of RBT-positivity.[24] One senior surgeon with the highest mastectomy performance rate in the trial and a long-standing experience in SSM and NSM in general performed the mastectomies with a significantly lower number of RBT-positive biopsies.

Regarding the type of surgery, we confirmed a significant higher rate of RBT under the NAC. This expected finding stresses that the indication for NSM has to be taken carefully in selected patients with sufficient tumour distance to the nipple and less tumour aggressiveness.

Another aspect that should be considered in the attempt to optimize surgical techniques to avoid RBT is the composition of the breast glandular surface. In this trial, pathologists measured the distance between surface of mastectomy specimens to breast tissue at five points and found inconsistent distances within the same breast between 0 mm and $>$ 10 mm. This finding supports the reports of Beer et al., who assessed the superficial layer (SL) that can be found between fat and breast tissue. They reported absence of SL in 56% of 62 examined breast specimens and the presence of irregular fascia with various glandular islands in 42% of the specimens.[28] Notably, Nickell and Skelton argued that there is no visible separation between fat and breast tissue.[29] With regard to the RBT-positive biopsies, however, we found that narrow

TABLE 2 Logistic regression model used to analyze factors related to RBT (biopsies included: A–O)

Risk factor	Coefficient β	*P*	Odds ratio	95% CI
Age (yr)	0.009	0.698	1.01	(0.97–1.06)
Body mass index (kg/m^2)	− 0.022	0.791	0.98	(0.83–1.15)
Breast weight (g)	− 0.001	0.518	0.99	(0.99–1)
Indication for mastectomy		0.376		
Curative (preinvasive carcinoma)	Reference			
Curative (invasive carcinoma)	0.654	0.363	1.92	(0.47–7.87)
Risk-reducing	− 0.493	0.641	0.61	(0.08–4.85)
Axilla surgery		0.608		
No axilla surgery	Reference			
Simultaneous sentinel node biopsy	− 0.678	0.475	0.51	(0.08–3.26)
Simultaneous axillary dissection	− 1.114	0.313	0.33	(0.04–2.86)
Previous sentinel node biopsy	− 1.913	0.106	0.15	(0.01–1.50)
Previous axillary dissection	− 0.788	0.559	0.46	(0.03–6.40)
Side of mastectomy (left vs. right)	0.159	0.721	1.17	(0.49–2.81)
Preoperative treatment		0.469		
No preoperative treatment	Reference			
Chemotherapy (CT)	− 1.029	0.258	0.36	(0.06–2.12)
Breast-conserving surgery (BCS)	0.873	0.282	2.39	(0.49–11.74)
Both (CT + BCS)	0.162	0.894	1.18	(0.11–12.94)
Surgeon		< 0.001		
Surgeon #1	Reference			
Surgeon #2	2.904	< 0.001	18.25	(4.28–77.82)
Surgeon #3	2.596	< 0.001	13.41	(4.03–44.61)
Surgeon #4	n.a.			
Surgeon #5	3.627	< 0.001	37.61	(6.91–205)
Surgeon #6	1.964	0.063	7.13	(0.90–56.67)
Surgeon #7	2.949	0.004	19.09	(2.53–144)
Incision type		0.902		
Periareolar	Reference			
Submammary fold	− 0.731	0.617	0.48	(0.03–8.45)
6 o'clock	− 0.073	0.966	0.93	(0.03–25.63)
Radial (upper outer quadrant)	0.349	0.807	1.42	(0.09–23.34)
Mixed (periareolar radial)	0.676	0.589	1.97	(0.17–22.78)
Other	0.18	0.904	1.20	(0.07–22.07)
Type of mastectomy (SSM vs. NSM)	2.594	< 0.001	13.39	(4.39–40.80)
Skin flap necrosis (no vs. yes)	− 0.846	0.207	0.43	(0.12–1.60)

n.a. not analyzed, low number of observations

distance (< 1 mm) between specimen surface and specimen breast tissue was significantly associated with higher RBT rates in the skin envelope.

Skin flap necrosis due to microvascular disorders (as defined by the Skin Score) is one of the most severe complications of SSM and NSM.[27] In our study, the hypothesis that a more radical surgery (e.g., complete absence of histologically detected RBT) leads to a higher rate of skin flap necrosis was not confirmed.

In conclusion, this trial demonstrated that RBT underneath the skin envelope after SSM and NSM is a frequent phenomenon, especially behind the nipple. However, we observed that highly experienced surgeons can perform SSM and NSM more radically under concomitant preservation of a low rate of skin flap necrosis. This suggests that intensive training of surgeons less experienced in SSM and NSM may lead to more radical surgical techniques that are not associated with increased rates of skin flap necrosis. However, the variable surface character of the breast gland poses anatomical limitations to the removal of the entire

breast tissue.[28,29] Thus, the interplay of surgical technique and patient-specific anatomic conditions is central to the frequently observed phenomenon of RBT after SSM and NSM. We argue that future prospective studies should include additional preoperatively assessed anatomical factors, such as subcutaneous flap properties, that might influence the presence of RBT after SSM or NSM.

Notably, the clinical relevance of RBT after SSM and NSM remains elusive, given previous findings suggesting that local recurrence might be more strongly associated with tumour biology and tumour aggressiveness than with surgical technique.[30,31] It is reasonable to assume that patients with aggressive tumours, high risk of local recurrence, or genetic predisposition might benefit from intensive postmastectomy follow-up that includes RBT detection. As shown in recent studies, the presence of RBT can be reliably assessed by postoperative MRI of the reconstructed breast.[32–35] For example, Woitek et al. detected RBT in up to 50% of all breasts after NSM and 13% after SSM.[32] These considerations and our results of the RBT-frequency after SSM and NSM led us to adapt the current wording from "prophylactic mastectomy" to "risk-reducing mastectomy" in the communication with our patients to prevent unrealistic perceptions concerning the efficacy of the surgical procedures. Furthermore, long-term, follow-up studies are warranted to reliably judge the true risk of cancer incidence or recurrence in cases with RBT.

ACKNOWLEDGMENT The authors thank the participating patients who made this study possible. The authors thank the surgical staff of the involved hospitals for their support and patience. The authors also thank A. Beccarelli, M. Brück, and M. von Wantoch for patient data registration and administration and A. Papassotiropoulos for statistical and scientific input. The study was supported by the Estée Lauder Breast Cancer Research Foundation.

Funding Estée Lauder Breast Cancer Research Foundation.

DISCLOSURES The authors declare no conflict of interest.

REFERENCES

1. Evans DG, Barwell J, Eccles DM, et al. The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services. *Breast Cancer Res.* 2014;16(5):442.
2. Galimberti V, Vicini E, Corso G, et al. Nipple-sparing and skin-sparing mastectomy: review of aims, oncological safety and contraindications. *Breast.* 2017;34(Suppl 1):S82–4.
3. Lanitis S, Tekkis PP, Sgourakis G, Dimopoulos N, Al Mufti R, Hadjiminas DJ. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg.* 2010;251(4):632–9.
4. Singletary SE. Skin-sparing mastectomy with immediate breast reconstruction: the M. D. Anderson Cancer Center experience. *Ann Surg Oncol.* 1996;3(4):411–6.
5. Kroll SS, Schusterman MA, Tadjalli HE, Singletary SE, Ames FC. Risk of recurrence after treatment of early breast cancer with skin-sparing mastectomy. *Ann Surg Oncol.* 1997;4(3):193–7.
6. Carlson GW, Bostwick J, 3rd, Styblo TM, et al. Skin-sparing mastectomy. Oncologic and reconstructive considerations. *Ann Surg.* 1997;225(5):570–5 (**discussion 575–8**).
7. Toth BA, Lappert P. Modified skin incisions for mastectomy: the need for plastic surgical input in preoperative planning. *Plast Reconstr Surg.* 1991;87(6):1048–53.
8. Sisco M, Yao KA. Nipple-sparing mastectomy: a contemporary perspective. *J Surg Oncol.* 2016;113(8):883–90.
9. Hudson DA, Skoll PJ. Single-stage, autologous breast restoration. *Plast Reconstr Surg.* 2001;108(5):1163–71 (**discussion 1172–3**).
10. Gerber B, Krause A, Reimer T, et al. Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg.* 2003;238(1):120–7.
11. Feron JG, Leduey A, Mallon P, et al. [The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature]. *Ann Chir Plast Esthet.* 2014;59(5):333–43.
12. Galimberti V, Morigi C, Bagnardi V, et al. Oncological outcomes of nipple-sparing mastectomy: a single-center experience of 1989 patients. *Ann Surg Oncol.* 2018;25(13):3849–57.
13. Sacchini V, Pinotti JA, Barros AC, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg.* Nov 2006;203(5):704–14.
14. 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;22(10):3241–9.
15. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch Plast Surg.* 2016;43(4):328–38.
16. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. 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):461–8.
17. 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;140(3):545–55.
18. Agrawal A, Sibbering DM, Courtney CA. Skin sparing mastectomy and immediate breast reconstruction: a review. *Eur J Surg Oncol.* 2013;39(4):320–8.
19. Missana MC, Laurent I, Germain M, Lucas S, Barreau L. Long-term oncological results after 400 skin-sparing mastectomies. *J Visc Surg.* 2013;150(5):313–20.
20. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol.* 2008;34(2):143–8.
21. Sakurai T, Zhang N, Suzuma T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. *Med Oncol.* 2013;30(1):481.
22. Weber WP, Haug M, Kurzeder C, et al. Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. *Breast Cancer Res Treat.* Sep 4 2018.

23. Torresan RZ, dos Santos CC, Okamura H, Alvarenga M. Evaluation of residual glandular tissue after skin-sparing mastectomies. *Ann Surg Oncol.* 2005;12(12):1037–44.
24. Dreadin J, Sarode V, Saint-Cyr M, Hynan LS, Rao R. Risk of residual breast tissue after skin-sparing mastectomy. *Breast J.* 2012;18(3):248–52.
25. Slavin SA, Schnitt SJ, Duda RB, et al. Skin-sparing mastectomy and immediate reconstruction: oncologic risks and aesthetic results in patients with early-stage breast cancer. *Plast Reconstr Surg.* 1998;102(1):49–62.
26. Reynolds C, Davidson JA, Lindor NM, et al. Prophylactic and therapeutic mastectomy in BRCA mutation carriers: can the nipple be preserved? *Ann Surg Oncol.* 2011;18(11):3102–9.
27. Lemaine V, Hoskin TL, Farley DR, et al. Introducing the SKIN score: a validated scoring system to assess severity of mastectomy skin flap necrosis. *Ann Surg Oncol.* 2015;22(9):2925–32.
28. Beer GM, Varga Z, Budi S, Seifert B, Meyer VE. Incidence of the superficial fascia and its relevance in skin-sparing mastectomy. *Cancer.* 2002;94(6):1619–25.
29. Nickell WB, Skelton J. Breast fat and fallacies: more than 100 years of anatomical fantasy. *J Hum Lact.* 2005;21(2):126–30.
30. Carlson GW, Styblo TM, Lyles RH, et al. Local recurrence after skin-sparing mastectomy: tumor biology or surgical conservatism? *Ann Surg Oncol.* 2003;10(2):108–12.
31. Petit JY, Veronesi U, Orecchia R, et al. Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia. *Ann Oncol.* 2012;23(8):2053–8.
32. Woitek R, Pfeiler G, Farr A, et al. MRI-based quantification of residual fibroglandular tissue of the breast after conservative mastectomies. *Eur J Radiol.* 2018;104:1–7.
33. Giannotti DG, Hanna SA, Cerri GG, Bevilacqua JLB. Analysis of skin flap thickness and residual breast tissue after mastectomy. *Int J Radiat Oncol Biol Phys.* 2018;102(1):82–91.
34. Hadar T, Tahover E, Gekhtman D, et al. MRI demonstration of distribution and extent of residual breast tissue in skin-sparing mastectomy with immediate reconstruction. Paper presented at: 19th annual meeting 2018; Orlando, FL.
35. Pfeiler G, Farr A, Woitek R, et al. Residual breast tissue after mastectomy in non high risk and BRCA mutated patients. *J Clin Oncol.* 2015;33(15).