Abstract

Purpose

Skin-sparing and nipple-sparing mastectomies (SSM; NSM) remove the breast's fibroglandular tissue (FGT), thereby reducing breast cancer risk. The postoperative presence of residual FGT (RFGT) is associated with remaining cancer risk. This study evaluated the role of MRI in the quantitative assessment of RFGT and its impact on the estimation of the remaining breast cancer risk.

Methods

The postoperative MRI scans (following EUSOMA recommendations) of 58 patients who had undergone SSM or NSM between 2003 and 2013, as well as preoperative MRI scans that were available in 25 of these patients, were retrospectively evaluated for the presence and location of RFGT by three radiologists. Two different observers quantitatively assessed the volume and percentage of retromamillary and other RFGT ($RFGT_{rm}$ and $RFGT_{other}$) were assessed. The Fisher's exact test, the Student's t-test, and intraclass coherence were used to compare patient groups and to assess reproducibility.

Results

RFGT was found in 20% of all breasts and significantly more frequently after NSM than SSM (50% vs. 13%, p=0.003). $RFGT_{rm}$ and $RFGT_{other}$ were more prevalent after NSM ($p < 0.001$; p=0.127). RFGT ranged from 0.5 to 26% of the preoperative FGT, with higher percentages after NSM than SSM (p = 0.181).

Conclusions

The prevalence and percentage of RFGT found on MRI indicate a considerable remaining postoperative breast cancer risk in some women.

Keywords

- Magnetic Resonance Imaging
- Mastectomy
- Breast cancer
- Imaging
- Mammary Glands

Abbreviations

BRCA1/2	BReast CAncer 1 and 2
cc	cubic centimeters
EUSOMA	European Society of Breast Cancer Specialists
FA	flip angle
FFE	fast field echo
FGT	fibroglandular tissue
FLASH	fast low angle shot
FOV	field of view
ICC	intraclass coherence
max	maximum
min	minimum
mm	millimeters
MRI	magnetic resonance imaging
ms	milliseconds
n	number
NAC	nipple-areola complex
NSM	nipple-sparing mastectomy
r	Pearson correlation coefficient
RFGT	residual fibroglandular tissue
RFGTother	residual fibroglandular tissue in other areas of the breast
RFGTrm	retromamillary residual fibroglandular tissue
SL	slice thickness
SSM	skin-sparing mastectomy
std	standard deviation
STIR	short tau inversion recovery
TDLUs	terminal duct lobular units
TE	echo time
TI	inversion time
TIRM	turbo inversion recovery magnitude

TR	repetition time
TSE	turbo spin echo

Introduction

In patients at high risk for developing breast cancer, such as BRCA1/2 (BReast CAncer 1 and 2) mutation carriers and women with a strong family history suggestive of hereditary breast cancer, mastectomy is frequently performed to remove the breast's fibroglandular tissue (FGT), thereby reducing breast cancer risk by 90-100% [1–5]. Skin-sparing mastectomy (SSM) includes the removal of the FGT and the nipple-areola complex (NAC) through a periareolar incision with lateral extension, while leaving a skin envelope (optimally ≤5mm thick [6,7]). This allows immediate reconstruction with subpectoral implants or autologous tissue [1,8,9]. SSM is performed not only for prophylactic reasons, but also for breast cancer in case of multicentricity or when postoperative breast irradiation is contraindicated [9]. SSM is supported by the results of a large series of cancer patients who did not show higher failure rates than those with skin-ablating mastectomy [10–13]. Despite several techniques for postoperative nipple reconstruction, the results are often unsatisfactory to the patient [14]. Thus, nipple-sparing mastectomy (NSM) has emerged as an alternative to SSM, in which the NAC is left in situ after it has been 'cored' (inverted and pruned of attaching glandular tissue, optimally ≤2-3mm thick [6]) [8]. It has previously been shown that preservation of the NAC with immediate reconstruction is psychosocially beneficial and that the inability to preserve the NAC may impede patients from undergoing prophylactic mastectomy [15–19]. The oncologic safety of NSM, especially in patients at high risk for breast cancer, is still under debate. Several retrospective studies showed encouraging results [8,20–22] while, other reports of limited effectiveness exist in rare cases [2,6,23], and there are few studies that document the long-term oncological safety of NSM in high-risk patients. The presumed oncological risk purportedly lies in the potentially remaining FGT within the NAC in NSM and in the skin flap after both SSM and NSM. Histopathological examinations showed that

terminal duct lobular units (TDLUs) are found in 60% of skin flaps after SSM, with the risk of residual TDLUs higher in skin flaps more than 5mm thick [7]. After NSM, TDLU density was shown to be even higher in the NAC than in the adjacent skin [24].

Previously published meta-data show that the overall incidence of breast cancer after prophylactic mastectomy is at least 0.7% per patient or 0.35% per breast, during follow-up periods between 10.4 to 168 months [8]. Data on longer follow-up periods, however, are still lacking. Recurrences after prophylactic mastectomies have been attributed to substantial amounts of residual fibroglandular tissue (RFGT) [25], and avoiding RFGT may therefore be crucial for the effectiveness of risk-reducing mastectomies.

Magnetic resonance imaging (MRI) offers the highest soft tissue contrast among breast imaging techniques at high spatial resolution, has shown to be the optimal screening tool in high risk patients and has been shown to allow quantification of FGT [26–28]. Quantification of RFGT, with a comparison to presurgical amounts of FGT, might, for the first time, allow a more personalized estimate of the remaining risk of breast cancer in patients who undergo SSM or NSM.

Therefore, this study evaluated the role of MRI in the quantitative assessment of RFGT and its impact on the estimation of the remaining postoperative breast cancer risk.

Materials and Methods

This retrospective, single-center study was approved by our institutional review board. The necessity for informed consent was waived. All patients who had undergone conservative mastectomies (SSM or NSM) with immediate implant-based reconstruction at our institution between 2003 and 2013 were retrospectively identified (n=157) and patients without postoperative MRI scans were excluded (n=99). Fifty-eight patients who had undergone postoperative MRI at our institution were included (in 25 patients preoperative MRI scans were also available, acquired 599±306 days before the postoperative MRI).

Postoperative MRI scans were obtained on 1.5 and 3 Tesla (T) units of different vendors, using dedicated breast coils, and included the acquisition of T1- and T2-weighted sequences in compliance with the EUSOMA (European Society of Breast Cancer Specialists) recommendations [29] (for detailed MRI sequence specifications see **Supplementary Material 1**). Sixty-six examinations (79.5%) were acquired using Siemens MAGNETOM scanners (Erlangen, Germany) and 17 examinations (20.5%) were acquired on Philips Scanners (Philips Medical Systems, Best, The Netherlands). All available unenhanced T1- and T2-weighted MR sequences were retrospectively evaluated. **Supplementary Material 2** provides patient characteristics, including age at surgery, type and side of surgery, reason for surgery, whether hereditary breast and ovarian cancer (HBOC) was diagnosed based on genetic testing, breast density, and body mass index (BMI) in the year of surgery. Breast density was assessed on preoperative MRI and mammograms or in the non-operated breast on postoperative MRI and on mammograms, if available, according to the ACR BI-RADS Atlas [30]. There was no discordance between density on MRI or mammograms. In cases of bilateral mastectomies and no preoperative MRI, preoperative mammograms alone were used to assess density.

Image analyses:

All pre- and postoperative unenhanced T1- and T2-weighted MRI sequences were evaluated independently by three experienced breast radiologists for **hypointensities suggestive of RFGT** due to the characteristic morphology of FGT, which consists of a mixture of patchy and linear hypointensities compared to surrounding hyperintense fatty tissue (**Figure 1a-d**). The reference standard for the presence of RFGT was a consensus reading by two dedicated breast radiologists using all the available pre- and postoperative T1- and T2-weighted sequences. The presence of hypointensities suggestive of FGT and the locations were noted. RFGT was noted as either retromamillary ($RFGT_{rm}$) when found in the area centred behind the nipple-areola complex with a diameter of 3 cm (**Figure 1a**). In other, more peripheral areas of the breast, RFGT was classified as $RFGT_{other}$, if seen (**Figure 1b and c**). The quadrant where $RFGT_{other}$ was found was noted as well.

Volumetry of the FGT and RFGT was performed by one radiologist using the standard software ImageJ (1.49v, National Institutes of Health, Bethesda, MD) by manually outlining the hypointensities on each slice, and calculating their volume (volume [cc] = (area [cm] x slice thickness [cm]) (**Figure 1e-g**). Hypointensities >1cc were considered positive for RFGT to avoid the inclusion of Cooper's ligaments instead of FGT. In those breasts considered positive for RFGT after this first round of assessment, a second observer performed volumetry of the RFGT independently to assess interobserver variability.

In nine breasts (eight patients) positive for RFGT, preoperative MRI scans were available. In these breasts, one radiologist quantified the preoperative FGT, as described above, and the percentage of unremoved FGT was calculated (% = RFGT [cc]/ preoperative FGT [cc] x 100).

Maximum skin envelope thickness was measured independently by two observers on axial T2-weighted MR images perpendicularly to the implant surface, leaving out the axillary tail (**Figure 1h**). The rationale behind this measurement is that the presence of TDLUs has been shown to vary depending on envelope thickness [7]. After analyses for interobserver variability, measurements acquired by Observer A were used for statistical analysis.

Statistics

SPSS 23.0 (SPSS, IBM, USA) was used for statistical analyses. Chi²-tests and Fisher's exact tests were used to compare patient groups with regard to the presence of RFGT . Student's t-tests and Mann-Whitney-U tests for independent samples were used to test for differences with regard to metric data with normal and non-normal distributions. The Kruskal-Wallis test was used to evaluate differences between different surgeons. Interobserver variability for metric data (volume of RFGT and envelope thickness) was assessed using Bland-Altman plots, and Pearson coefficients were calculated for correlations between measurements obtained by different observers and for correlations between the mean and standard deviation of the measurements. Nominal data (presence of RFGT) were assessed for agreement among three observers by calculating intraclass coherence (ICC) and 95% confidence intervals. P-values below 0.05 were considered significant.

Results

Patients and surgeries

Mean patient age among the 58 patients was 44.2±10.0 years at surgery and 46.1±10.7 years at postoperative MRI.

In 28/58 patients (48.3%), mastectomies were bilateral (21 SSM; 7 NSM; for detailed descriptive statistics see **Table 1**).

SSM was significantly more likely to be therapeutic and NSM to be prophylactic ($p<0.001$).

No significant difference between SSM and NSM was found with regard to breast density ($p=0.499$). BMI was significantly higher in patients who had undergone SSM (mean=42.6; std=8.2) than in patients who had undergone NSM (mean=36.4; std=3.7; $p=0.026$) (Supplementary Material 2 and 3).

The diagnosis of HBOC in 23 patients was based on genetic testing. Of those patients, 14 had bilateral prophylactic mastectomies. One patient (ID 29) had bilateral breast cancer, and, therefore, had therapeutic bilateral mastectomies. In seven patients with HBOC and breast cancer, mastectomy was therapeutic in one breast and prophylactic in the contralateral breast. One patient (ID 31) with HBOC and breast cancer declined prophylactic contralateral mastectomy and had unilateral therapeutic mastectomy only, despite counseling (Supplementary Material 2).

Residual fibroglandular tissue (RFGT)

Presence of RFGT

RFGT was found in 20.0% (17/85) of all breasts (**Table 2; Figure 2**). In the subgroup of NSM, significantly more patients (50.0%; 8/16) had RFGT compared to SSM (13.0%; 9/69) (p=0.003). The higher prevalence of RFGT after NSM was partly due to retromamillary RFGT ($RFGT_{rm}$, which was found only after NSM in 43.8% [7/16]), but not after SSM (p < 0.001). However, RFGT in other areas of the breast was also more frequently encountered after NSM (31.3%) than SSM (13.0%), although this difference was not significant (p=0.127).
In only one of 28 bilaterally operated patients was RFGT found bilaterally ($RFGT_{rm}$ after bilateral NSM).
Higher volumes of $RFGT_{rm}$ were found after prophylactic mastectomies than after therapeutic mastectomies (p<0.001) (Supplementary Material 3), with NSM the only type of mastectomy associated with $RFGT_{rm}$ and the more being more frequently performed for prophylactic indications than SSM. BMI was not significantly different between patients with and without RFGT (p=0.560) or $RFGT_{other}$ (p=0.507).

$RFGT_{rm}$ showed an almost significant negative correlation with age (r = -0.471; p = 0.056) since $RFGT_{rm}$ was observed only after NSM, which, in turn, was more frequently performed for prophylactic reasons in presumably younger patients.

No significant differences were noted between the 13 surgeons who operated on one to 19 of our 58 included patients with regard to the presence of RFGT (p=0.586), $RFGT_{rm}$ (p=0.345), or $RFGT_{other}$ (p=0.984). Between different indications (prophylactic or therapeutic), no

significant differences were found with regard to the presence of RFGT (p=0.346), $RFGT_{rm}$ (p=0.087), or $RFGT_{other}$ (p=0.518).

Breasts with RFGT: The volume of RFGT and its location

Among breasts positive for RFGT, the mean volume of RFGT was 4.4 ± 3.7cc and was similar after SSM and NSM (p=0.922) (**Table 3**). $RFGT_{rm}$ was exclusively found after NSM, and, among those breasts positive for $RFGT_{rm}$, the mean volume was 1.9±1.3cc. $RFGT_{other}$ reached a mean volume of 4.2±3.6 cc, with similar results after SSM and NSM (p=0.942).

RFGT was most frequently found in the craniolateral and caudolateral quadrants (64.3% and 35.7%) (**Table 4; Figure 3**). No significant difference between NSM and SSM was noted with regard to the location of the RFGT (p=0.305).

Breasts with RFGT: percentage of unremoved FGT

In nine patients with RFGT and preoperative MRI scans, the preoperative volume of FGT was calculated (mean = 123.2 ± 78.5 cc). The mean percentage of unremoved FGT was 5.8 ± 8.2%, but these results varied strongly (0.5 – 26.9%) (**Table 5**). After NSM, the percentage of unremoved FGT was generally higher (7.9 ± 9.7%) than after SSM (1.7 ± 0.1%), although the difference did not reach the level of significance (p = 0.181). Of note, after NSM, the percentage of unremoved FGT constituted by $RFGT_{other}$ was similar to that by $RFGT_{rm}$ (4.0% versus 3.8%; p=0.935). Furthermore, $RFGT_{other}$ constituted a higher percentage of unremoved FGT after NSM than after SSM (4.0% versus 1.7%; p=0.483).

No significant correlation between the volumes of preoperative FGT and of RFGT (p = 0.405; k = -0.318) or the percentage of RFGT (p = 0.120; k = -0.556) was found.

Envelope thickness

Mean envelope thickness was 13.2 ± 9.2mm (range 2–39mm). There was no significant correlation of envelope thickness with RFGT (p=0.064; k=0.563), $RFGT_{other}$ (p=0.300; k= 0.114), or $RFGT_{rm}$ (p=0.216; k=-0.136).

Interrater reliability

Three readers reached substantial to excellent agreement with regard to the presence of RFGT (ICC: 0.818; 95% CI: 0.752-0.870).

In all breasts positive for RFGT, two readers performed volumetry of the RFGT and interrater reliability was assessed (**Supplementary Material 4 and 5**). Correlation between measurements by the two readers was significant (p<0.001; r=0.97), whereas the difference

between the measurements did not correlate significantly with the mean volume (p=0.529; r=-0.164).

Maximum skin envelope thickness was measured by two readers in all breasts and interrater reliability was assessed (**Supplementary Material 4 and 5**). Correlation between measurements obtained by the two readers was significant (p<0.001; r=0.98), whereas the difference between the measurements did not correlate significantly with the mean thickness (p=0.244; r=-0.128).

Discussion

Our study shows that MRI is able to identify RFGT in up to 50% of all breasts after NSM and 13% after SSM, reaching an overall prevalence of 20% after conservative mastectomies. Not only $RFGT_{rm}$, but also $RFGT_{other}$, is more frequently found after NSM than SSM (31% vs. 13%). Comparisons of pre- and postoperative MRI scans showed that higher proportions of unremoved FGT are found after NSM than after SSM (7.9% versus 1.7%). Of note, $RFGT_{rm}$, which was found only after NSM did not totally account for that difference, but rather, $RFGT_{other}$ which was also left in higher proportions after NSM than after SSM (4.8% versus 1.7%). However, most of these differences between NSM and SSM (especially with regard to $RFGT_{other}$) did not reach the level of significance. Nevertheless, our results emphasize the necessity for improved surgical planning and technique, since NSM and SSM are frequently performed for prophylactic indications in women at high risk for breast cancer. Particularly in these patients, removal of as much FGT as possible is crucial in order to justify surgery with all its psychosocial and physical implications for otherwise healthy individuals. Preoperative interdisciplinary meetings between surgeons and radiologists who evaluate the distribution and extent of FGT based on preoperative MRI might improve the postoperative outcome. For this retrospective study, MRI was chosen as a modality because it has been shown previously to allow highly robust and reproducible quantification of FGT [31]. Furthermore, MRI depicts the entire breast, including the axillary tail and far medial and lateral breast areas without superimpositions, which often occur on mammograms, especially after implant-based reconstructions. A retrospective analysis of postoperative ultrasound images might be limited too severely to the images saved by the examiner whose focus may not have been on RFGT, but rather, on the detection of recurrence. For this study, MRI was the best choice, but, for future prospective studies on RFGT, other modalities, including ultrasound and automated breast ultrasound (ABUS), might be a good alternative

to MRI. This is the first study to indicate the percentage of RFGTderived from quantitative image analysis based on the high soft-tissue contrast of MRI, as well as the depiction of all areas of the breast even far medial or lateral areas, together with the entire axillary tail without any superimpositions, such as those seen on mammography.

Although NSM is more and more widely accepted as an equally safe alternative to SSM, with a more favorable aesthetic outcome, some controversy concerning the postoperative risk of breast cancer development or recurrence still exists [1,2,6,8,23]. Usually, there is concern about the amount of RFGT that remains in situ in the retromamillary area. Thus, a high prevalence of $RFGT_{rm}$ after NSM was anticipated by the authors of this study and our findings confirmed this hypothesis. But even more importantly, other areas of the breast are also more often affected by RFGT after NSM than after SSM, and the volume of $RFGT_{other}$ is also higher after NSM than SSM, albeit not significantly. These differences in prevalence and volume of $RFGT_{other}$ may shift our concerns away from the NAC toward the more peripheral areas of the breast to attempt optimal cancer risk reduction after NSM as well. Possibly, the results indicate differences between NSM and SSM with regard to surgical accessibility. The more limited linear incision in NSM may not allow the removal of as much FGT as in SSM with its circular incision around the areola. The locations where $RFGT_{other}$ was found were similar after NSM and SSM, with the craniolateral quadrant a frequent location of RFGT. In the caudolateral quadrant, $RFGT_{other}$ was frequently found after SSM, but not after NSM, possibly suggesting a better access to this area during NSM.

Envelope thickness frequently exceeded the recommended 5mm and did not correlate significantly with the amount of RFGT. This finding emphasizes the importance of dedicated preoperative planning rather than simply attempting to keep the skin envelope as thin as possible. Whenever safely possible, a thicker skin envelope poses less risk of postoperative complications, such as skin necrosis, but needs to be weighed against the risk of reasonable amounts of RFGT. Preoperative surgical planning may thus help with the presurgical estimation of a suitable envelope thickness for each patient individually.

The presence of RFGT or the amount did not depend on the indications for surgery (therapeutic or prophylactic), nor on the surgeon. Thus, RFGT seems to be a risk inherent to the surgical procedure itself and needs to be addressed by meticulous preoperative evaluation of the location and distribution of FGT. The increased use of preoperative MRI—in the prophylactic as well as in the therapeutic setting—may allow excision of the FGT without leaving relevant amounts behind. Preoperative MRI that would, ideally, be discussed among radiologists and surgeons, with a special emphasis on the amount and distribution of FGT, might allow a modification of the surgical technique to target the surgeon's attention to specific areas that might require more extensive removal of tissue than that which is performed during a standard approach, as might be the case for the periphery of the breast. In addition, postoperative MRI, or even standard handheld ultrasound or automated breast ultrasound (ABUS), might be of use to exclude RFGT and to identify patients who might benefit from additional removal of any RFGT.

The limitations of this study are the relatively small sample size, although this was limited by the number of mastectomies performed at our institution and the availability of postoperative MRI. Clearly, a follow-up study with prospective acquisition of pre- and

postoperative MRI would be of benefit to increase the sample size and to evaluate the effect of prior knowledge about the amount and distribution of FGT on RFGT. FGT volumetry was performed manually. However, in the postoperative breast, there is currently no software available to perform the necessary measurements fully automatically. Our study lacks pathohistological verification. However, it has been shown previously that TDLUs can be found in the breast after mastectomy [7,24].

In conclusion, our study identifies a relatively high prevalence of RFGT after conservative mastectomies (especially after NSM) and high proportions of unremoved FGT in some individuals. It shows that, with improper surgical planning, breast cancer risk might still be elevated, even after risk-reducing surgery, in patients with high amounts of RFGT. MRI-based interdisciplinary surgical planning—involving the radiologist and the surgeon—should take into account the amount, location, and distribution of the FGT. This preoperative planning may, in the future, improve the oncologic safety of NSM and SSM and increase the patients' benefit from these surgical procedures. Furthermore, postoperative MRI assessment allows the estimation of the remaining cancer risk in individual patients, and surgeons are advised to inform the patient that RFGT has been quantified and constitutes a remaining breast cancer risk.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

[1] J.G. Guillem, W.C. Wood, J.F. Moley, A. Berchuck, B.Y. Karlan, D.G. Mutch, R.F. Gagel, J. Weitzel, M. Morrow, B.L. Weber, F. Giardiello, M.A. Rodriguez-Bigas, J. Church, S. Gruber, K. Offit, ASCO, SSO, ASCO/SSO Review of Current Role of Risk-Reducing Surgery in Common Hereditary Cancer Syndromes, J. Clin. Oncol. 24 (2006) 4642–4660. doi:10.1200/JCO.2005.04.5260.

[2] L.C. Hartmann, T.A. Sellers, D.J. Schaid, T.S. Frank, C.L. Soderberg, D.L. Sitta, M.H. Frost, C.S. Grant, J.H. Donohue, J.E. Woods, S.K. McDonnell, C.W. Vockley, A. Deffenbaugh, F.J. Couch, R.B. Jenkins, Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers., J. Natl. Cancer Inst. 93 (2001) 1633–7. http://www.ncbi.nlm.nih.gov/pubmed/11698567 (accessed February 7, 2017).

[3] B.A.M. Heemskerk-Gerritsen, M.B.E. Menke-Pluijmers, A. Jager, M.M.A. Tilanus-Linthorst, L.B. Koppert, I.M.A. Obdeijn, C.H.M. van Deurzen, J.M. Collée, C. Seynaeve, M.J. Hooning, Substantial breast cancer risk reduction and potential survival benefit after bilateral mastectomy when compared with surveillance in healthy BRCA1 and BRCA2 mutation carriers: a prospective analysis., Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 24 (2013) 2029–35. doi:10.1093/annonc/mdt134.

[4] R. Kaas, S. Verhoef, J. Wesseling, M.A. Rookus, H.S.A. Oldenburg, M.-J.V. Peeters, E.J.T. Rutgers, Prophylactic mastectomy in BRCA1 and BRCA2 mutation carriers: very low risk for subsequent breast cancer., Ann. Surg. 251 (2010) 488–92. doi:10.1097/SLA.0b013e3181c3c36d.

[5] T.R. Rebbeck, T. Friebel, H.T. Lynch, S.L. Neuhausen, L. van ’t Veer, J.E. Garber, G.R. Evans, S.A. Narod, C. Isaacs, E. Matloff, M.B. Daly, O.I. Olopade, B.L. Weber, Bilateral Prophylactic Mastectomy Reduces Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The PROSE Study Group, J. Clin. Oncol. 22 (2004) 1055–1062. doi:10.1200/JCO.2004.04.188.

[6] V. Sacchini, J.A. Pinotti, A.C.S.D. Barros, A. Luini, A. Pluchinotta, M. Pinotti, M.G. Boratto, M.D. Ricci, C.A. Ruiz, A.C. Nisida, P. Veronesi, J. Petit, P. Arnone, F. Bassi, J.J. Disa, C.A. Garcia-Etienne, P.I. Borgen, Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem?, J. Am. Coll. Surg. 203 (2006) 704–14. doi:10.1016/j.jamcollsurg.2006.07.015.

[7] R.Z. Torresan, C.C. dos Santos, H. Okamura, M. Alvarenga, Evaluation of residual glandular tissue after skin-sparing mastectomies., Ann. Surg. Oncol. 12 (2005) 1037–44. doi:10.1245/ASO.2005.11.027.

[8] V.M.T. van Verschuer, M.C. Maijers, C.H.M. van Deurzen, L.B. Koppert, Oncological safety of prophylactic breast surgery: skin-sparing and nipple-sparing versus total mastectomy., Gland Surg. 4 (2015) 467–75. doi:10.3978/j.issn.2227-684X.2015.02.01.

[9] A.T. Manning, V.S. Sacchini, Conservative mastectomies for breast cancer and risk-reducing surgery: the Memorial Sloan Kettering Cancer Center experience., Gland Surg. 5 (2016) 55–62. doi:10.3978/j.issn.2227-684X.2015.10.02.

[10] G.W. Carlson, J. Bostwick, T.M. Styblo, B. Moore, J.T. Bried, D.R. Murray, W.C. Wood, Skin-sparing mastectomy. Oncologic and reconstructive considerations., Ann. Surg. 225 (1997) 570-5-8. http://www.ncbi.nlm.nih.gov/pubmed/9193184 (accessed February 7, 2017).

[11] G.W. Carlson, T.M. Styblo, R.H. Lyles, G. Jones, D.R. Murray, C.A. Staley, W.C. Wood, The use of skin sparing mastectomy in the treatment of breast cancer: The Emory experience, Surg. Oncol. 12 (2003) 265–269. doi:10.1016/j.suronc.2003.09.002.

[12] T.J. Meretoja, S. Rasia, K.A.J. von Smitten, S.L. Asko-Seljavaara, H.O.M. Kuokkanen, T.A. Jahkola, Late results of skin-sparing mastectomy followed by immediate breast reconstruction., Br. J. Surg. 94 (2007) 1220–5. doi:10.1002/bjs.5815.

[13] S.S. Kroll, A. Khoo, S.E. Singletary, F.C. Ames, B.G. Wang, G.P. Reece, M.J. Miller, G.R. Evans,

G.L. Robb, Local recurrence risk after skin-sparing and conventional mastectomy: a 6-year follow-up., Plast. Reconstr. Surg. 104 (1999) 421–5. http://www.ncbi.nlm.nih.gov/pubmed/10654685 (accessed February 7, 2017).

[14] M.A. Jabor, P. Shayani, D.R. Collins, T. Karas, B.E. Cohen, Nipple-areola reconstruction: satisfaction and clinical determinants., Plast. Reconstr. Surg. 110 (2002) 457-63–5. http://www.ncbi.nlm.nih.gov/pubmed/12142660 (accessed February 7, 2017).

[15] F. Didier, P. Arnaboldi, S. Gandini, A. Maldifassi, A. Goldhirsch, D. Radice, I. Minotti, B. Ballardini, A. Luini, B. Santillo, M. Rietjens, J.Y. Petit, Why do women accept to undergo a nipple sparing mastectomy or to reconstruct the nipple areola complex when nipple sparing mastectomy is not possible?, Breast Cancer Res. Treat. 132 (2012) 1177–84. doi:10.1007/s10549-012-1983-y.

[16] J.-Y. Petit, U. Veronesi, V. Lohsiriwat, P. Rey, G. Curigliano, S. Martella, C. Garusi, F. De Lorenzi, A. Manconi, E. Botteri, F. Didier, R. Orecchia, M. Rietjens, Nipple-sparing mastectomy--is it worth the risk?, Nat. Rev. Clin. Oncol. 8 (2011) 742–7. doi:10.1038/nrclinonc.2011.159.

[17] F. Didier, D. Radice, S. Gandini, R. Bedolis, N. Rotmensz, A. Maldifassi, B. Santillo, A. Luini, V. Galimberti, E. Scaffidi, F. Lupo, S. Martella, J.Y. Petit, Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality?, Breast Cancer Res. Treat. 118 (2009) 623–33. doi:10.1007/s10549-008-0238-4.

[18] R. Djohan, E. Gage, J. Gatherwright, S. Pavri, J. Firouz, S. Bernard, R. Yetman, Patient satisfaction following nipple-sparing mastectomy and immediate breast reconstruction: an 8-year outcome study., Plast. Reconstr. Surg. 125 (2010) 818–29. doi:10.1097/PRS.0b013e3181ccdaa4.

[19] K.A. Metcalfe, J.L. Semple, S.A. Narod, Time to reconsider subcutaneous mastectomy for breast-cancer prevention?, Lancet. Oncol. 6 (2005) 431–4. doi:10.1016/S1470-2045(05)70210-2.

[20] P. de Alcantara Filho, D. Capko, J.M. Barry, M. Morrow, A. Pusic, V.S. Sacchini, Nipple-sparing mastectomy for breast cancer and risk-reducing surgery: the Memorial Sloan-Kettering Cancer Center experience., Ann. Surg. Oncol. 18 (2011) 3117–22. doi:10.1245/s10434-011-1974-y.

[21] B. Gerber, A. Krause, M. Dieterich, G. Kundt, T. Reimer, The Oncological Safety of Skin Sparing Mastectomy with Conservation of the Nipple-Areola Complex and Autologous Reconstruction: An Extended Follow-Up Study, Ann. Surg. 249 (2009) 461–468. doi:10.1097/SLA.0b013e31819a044f.

[22] J.Y. Petit, U. Veronesi, R. Orecchia, G. Curigliano, P.C. Rey, E. Botteri, N. Rotmensz, V. Lohsiriwat, M. Cassilha Kneubil, M. Rietjens, Risk factors associated with recurrence after nipple-sparing mastectomy for invasive and intraepithelial neoplasia., Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 23 (2012) 2053–8. doi:10.1093/annonc/mdr566.

[23] L.C. Hartmann, D.J. Schaid, J.E. Woods, T.P. Crotty, J.L. Myers, P.G. Arnold, P.M. Petty, T.A. Sellers, J.L. Johnson, S.K. McDonnell, M.H. Frost, C.S. Grant, V. V. Michels, R.B. Jenkins, Efficacy of Bilateral Prophylactic Mastectomy in Women with a Family History of Breast Cancer, N. Engl. J. Med. 340 (1999) 77–84. doi:10.1056/NEJM199901143400201.

[24] V.M.T. van Verschuer, C.H.M. van Deurzen, P.J. Westenend, J. Rothbarth, C. Verhoef, E.J.T. Luiten, M.B.E. Menke-Pluijmers, L.B. Koppert, Prophylactic Nipple-sparing Mastectomy Leaves More Terminal Duct Lobular Units In Situ as Compared With Skin-sparing Mastectomy, Am. J. Surg. Pathol. 38 (2014) 706–712. doi:10.1097/PAS.0000000000000180.

[25] A.-B. Skytte, D. Crüger, M. Gerster, A.-V. Laenkholm, C. Lang, K. Brøndum-Nielsen, M. Andersen, L. Sunde, S. Kølvraa, A.-M. Gerdes, Breast cancer after bilateral risk-reducing mastectomy, Clin. Genet. 79 (2011) 431–437. doi:10.1111/j.1399-0004.2010.01604.x.

[26] G.J. Wengert, T.H. Helbich, R. Woitek, P. Kapetas, P. Clauser, P.A. Baltzer, W.-D. Vogl, M. Weber, A. Meyer-Baese, K. Pinker, Inter- and intra-observer agreement of BI-RADS-based subjective visual estimation of amount of fibroglandular breast tissue with magnetic

resonance imaging: comparison to automated quantitative assessment., Eur. Radiol. 26 (2016) 3917–3922. doi:10.1007/s00330-016-4274-x.

[27] C.C. Riedl, N. Luft, C. Bernhart, M. Weber, M. Bernathova, M.-K.M. Tea, M. Rudas, C.F. Singer, T.H. Helbich, Triple-modality screening trial for familial breast cancer underlines the importance of magnetic resonance imaging and questions the role of mammography and ultrasound regardless of patient mutation status, age, and breast density., J. Clin. Oncol. 33 (2015) 1128–35. doi:10.1200/JCO.2014.56.8626.

[28] X.-A. Phi, N. Houssami, I.-M. Obdeijn, E. Warner, F. Sardanelli, M.O. Leach, C.C. Riedl, I. Trop, M.M.A. Tilanus-Linthorst, R. Mandel, F. Santoro, G. Kwan-Lim, T.H. Helbich, H.J. de Koning, E.R. Van den Heuvel, G.H. de Bock, Magnetic resonance imaging improves breast screening sensitivity in BRCA mutation carriers age ≥ 50 years: evidence from an individual patient data meta-analysis., J. Clin. Oncol. 33 (2015) 349–56. doi:10.1200/JCO.2014.56.6232.

[29] F. Sardanelli, C. Boetes, B. Borisch, T. Decker, M. Federico, F.J. Gilbert, T. Helbich, S.H. Heywang-Köbrunner, W.A. Kaiser, M.J. Kerin, R.E. Mansel, L. Marotti, L. Martincich, L. Mauriac, H. Meijers-Heijboer, R. Orecchia, P. Panizza, A. Ponti, A.D. Purushotham, P. Regitnig, M.R. Del Turco, F. Thibault, R. Wilson, Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group., Eur. J. Cancer. 46 (2010) 1296–316. doi:10.1016/j.ejca.2010.02.015.

[30] V.A. Reston, The American College of Radiology (ACR) (2013) Breast Imaging Reporting and Data System Atlas (BI-RADS® Atlas), 2013.

[31] G.J. Wengert, T.H. Helbich, W.-D. Vogl, P. Baltzer, G. Langs, M. Weber, W. Bogner, S. Gruber, S. Trattnig, K. Pinker, Introduction of an automated user-independent quantitative volumetric magnetic resonance imaging breast density measurement system using the Dixon sequence: comparison with mammographic breast density assessment., Invest. Radiol. 50 (2015) 73–80. doi:10.1097/RLI.0000000000000102.

Tables and legends

					NSM		SSM	
n		**n**	**%**		**n**	***%***	**n**	***%***
58	**patients** with mastectomies with immediate implant-based reconstructions included	28	*48.3*	bilateral mastectomies	7	*12.1*	21	*36.2*
				n 13 bilateral prophylactic mastectomies 7 bilateral therapeutic mastectomies 7 unilateral therapeutic and contralateral prophylactic mastectomies 1 unilateral therapeutic mastectomy without reconstruction (breast excluded) and contralateral prophylactic mastectomy with reconstruction (included)				
		30	*51.7*	unilateral therapeutic mastectomies	2	*3.4*	28	*48.3*
					NSM		**SSM**	
					n	***%***	**n**	***%***
85	**breasts** included overall			42 right-sided/ 43 left-sided	16	*18.8*	69	*81.2*

Table 1. **Descriptive statistics of patients and breasts included in the study, with laterality of surgery and type of indication, as well as type of surgery.** n = number; NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy.

	Patients						Breasts						
	all surgeries		SSM		NSM		all surgeries		SSM		NSM		
	n	%	n	%	n	%	n	%	n	%	n	%	P
no RFGT	42	*72.41*	40	*81.6*	2	*22.2*	68	*80.0*	60	*87.0*	8	*50.0*	
RFGT	16	*27.6*	9	*18.7*	7	*77.8*	17	*20.0*	9	*13.0*	8	*50.0*	*0.003*
$RFGT_{rm}$	6	*10.3*	0	*0.0*	6	*66.7*	7	*8.2*	0	*0.0*	7	*43.8*	*<0.001*
$RFGT_{other}$	14	*24.2*	9	*18.4*	5	*55.6*	14	*16.5*	9	*13.0*	5	*31.3*	*0.127*
all	58	*100.0*	49	*84.5*	9	*15.5*	85	*100.0*	69	*81.2*	16	*18.8*	

Table 2. Prevalence of RFGT, $RFGT_{rm}$, and $RFGT_{other}$ per patient and per breast according to surgery type. n = number; SSM = skin-sparing mastectomy; NSM = nipple-sparing mastectomy; RFGT = residual fibroglandular tissue; $RFGT_{rm}$ = retromamillary residual fibroglandular tissue; $RFGT_{other}$ = other residual fibroglandular tissue.

[cc]	All				SSM		NSM		p
	mean	std	min	max	mean	std	mean	std	
RFGT	4.4	3.7	1.1	15	4.3	4.1	4.5	3.5	0.922
RFGTrm	1.9	1.3	1.0	3.8	0.0	0.0	1.9	1.3	<0.001
RFGTother	4.2	3.6	1.2	14.5	4.3	4.1	4.1	3.0	0.942

Table 3. Volumes of RFGT, $RFGT_{rm}$, and $RFGT_{other}$ in breasts with RFGT according to surgery type. Mean, std, min, and max were calculated taking into account only breasts with RFGT. cc = cubic centimeters; std = standard deviation; min = minimum; max = maximum; SSM = skin-sparing mastectomy; NSM = nipple-sparing mastectomy. RFGT = residual fibroglandular tissue; $RFGT_{rm}$ = retromamillary residual fibroglandular tissue; $RFGT_{other}$ = other residual fibroglandular tissue.

	all surgeries		NSM		SSM	
craniolateral	64.3%	9/14	100%	5/5	44.4%	4/9
craniomedial	21.4%	3/14	20%	1/5	22.2%	2/9
caudolateral	35.7%	5/14	0%	0/5	55.6%	5/9
caudomedial	14.3%	2/14	0%	0/5	22.2%	2/9

Table 4. **Location of $RFGT_{other}$ in 14 breasts (five after NSM and nine after SSM).** NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy.

		All					SSM *(3)*		NSM *(6)*		
		mean	**std**	**range**			**mean**	**std**	**mean**	**std**	**p**
preoperative FGT	[cc]	123.2	78.5	44.6	-	235.9	160.3	67.6	104.6	82.4	0.329
RFGT	[%]	5.8	8.2	0.5	-	26.9	1.7	0.1	7.9	9.7	0.181
$RFGT_{rm}$	[%]	2.5	3.2	0	-	7.8	0	0	3.8	3.2	*0.033*
$RFGT_{other}$	[%]	3.3	6.1	0	-	19.1	1.7	0.1	4.0	7.5	0.483

Table 5. **Volume of preoperative FGT in cc and percentage of unremoved FGT in nine breasts with RFGT and preoperative MRI.** cc = cubic centimeter; std = standard deviation; SSM = skin sparing mastectomy (3 breasts); NSM = nipple-sparing mastectomy (6 breasts); RFGT = residual fibroglandular tissue; $RFGT_{rm}$ = retromamillary residual fibroglandular tissue; $RFGT_{other}$ = other residual fibroglandular tissue.

Figure legends

Figure 1. **Examples of RFGT in different patients on T2-weighted axial images (a-c, e,f, and h) and preoperative FGT on T1-weighted axial images (d and g).** *a)* RFGT in the retromamillary area (**$RFGT_{rm}$**). *b)* and *c)* RFGT in other areas of the breast (**$RFGT_{other}$**). *d)* Preoperative FGT in the axillary tail [same breast as shown postoperatively in *c)]*. Quantification of $RFGT_{rm}$ (e), $RFGT_{other}$ (*f*), and preoperative FGT (*g*). Yellow lines outline the hypointense areas identified as RFGT for volumetry. *h*) Measurement of the envelope thickness perpendicularly to the implant surface.

Figure 2. Prevalence of RFGT, $RFGT_{rm}$, and $RFGT_{other}$ among all included breasts. SSM = skin-sparing mastectomy; NSM = nipple-sparing mastectomy; all = all surgeries (SSM and NSM); RFGT = residual fibroglandular tissue; $RFGT_{rm}$ = retromamillary residual fibroglandular tissue; $RFGT_{other}$ = other residual fibroglandular tissue.

Figure 3. **Schematic drawings indicating percentages of patients in whom $RFGT_{other}$ was found in the different breast quadrants after all surgeries (14 breasts), after SSM (nine breasts), and after NSM (five breasts).** SSM = skin-sparing mastectomy; NSM = nipple-sparing mastectomy.