



Residual glandular tissue (RGT) in *BRCA1/2* germline mutation carriers with unilateral and bilateral prophylactic mastectomies

Olga Grinstein^{a,1}, Barbara Krug^{a,*,1}, Martin Hellmic^b, Florian Siedek^a, Wolfram Malter^d, Christina Burke^a, Rita Schmutzler^c, David Maintz^a, Kerstin Rhiem^c

^a Department of Diagnostic and Interventional Radiology, University Hospital of Cologne, Germany

^c Center for Hereditary Breast and Ovarian Cancer, Center for Integrated Oncology (CIO), University of Cologne, Faculty of Medicine and University Hospital of Cologne, Germany

^b Institute of Medical Statistics and Bioinformatics, University of Cologne, Germany

^d Breast Center, Department of Gynaecology and Obstetrics, University Hospital of Cologne, Germany

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ABSTRACT

Background: Prophylactic mastectomy (PME) is increasingly performed in women carrying deleterious *BRCA1* and *BRCA2* germline mutations. The oncologic risk resulting from residual fibroglandular tissue (RGT) is unknown.

Methods: All women who had received a mastectomy and at least one postoperative breast MRI, between 2006 and 2016 were extracted from the register of the Center for Hereditary Breast and Ovarian Cancer Cologne (CHBOC). The index MRI was evaluated in terms of basic clinical data and the morphological criteria of RGT. The RGT volume was measured in diameter and was semi-automatically evaluated using software.

Results: We identified 169 women carrying *BRCA1/2* mutations who underwent prophylactic and curative mastectomy: a total of 338 breasts. RGT was found in 128 of the 338 breasts (37.9%). 68 of the 128 breasts (53.1%) were related to bilateral PME, 37 (28.9%) to unilateral PME and 23 (18.0%) to curative mastectomy. RGT was predominantly unifocal and located in the retroareolar breast region. RGT was observed more often after bilateral PME ($p < 0.0001$). In this subgroup, the nipple-sparing mastectomy dominated (108 of 136, 79.4%), in contrast to 23 standard mastectomies (23 of 94, 24.5%) in the subgroup of curative mastectomy (23%). There was a trend towards higher amounts of RGT in surgical units with fewer mastectomies performed. During follow-up, two breast cancers were detected after bilateral and unilateral PME, respectively.

Conclusions: Our results suggest that the indication for surgery and in particular the selected surgical procedure affect the surgical outcome with respect to RGT. Oncological safety should not be neglected, especially in the high-risk group of *BRCA1/2* mutation carriers.

1. Purpose

The risk of developing breast cancer by the age of 80 is estimated to be 44% to 79% for *BRCA1* mutation carriers and 18%–77% for *BRCA2* mutation carriers [1,2]. The risk of developing metachronous contralateral breast cancer is also increased depending on the mutated gene and the age of the patient at diagnosis [3,4]. *BRCA1* mutation carriers have a 30% higher mortality rate compared to patients with *BRCA1* negative and sporadic breast cancer [5]. *BRCA2* mutation carriers have a 29% poorer breast cancer specific survival compared to *BRCA2* negative breast cancer patients [5].

The relevance of structured, image-based surveillance is undisputed

in the light of this background [6–10]. The German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC), founded in 1996 by the German Cancer Aid, today comprises 19 specialized university centers throughout Germany. Since 2005 it has offered women at risk of breast cancer not only a detailed consultation with risk calculation and genetic testing but also a structured image-based surveillance program which includes an annual breast MRI [11,12]. As an alternative to participating in this image-based surveillance program, bilateral prophylactic mastectomy (PME) in healthy *BRCA1/2* mutation carriers and unilateral PME in *BRCA1/2* mutation carriers with history of contralateral breast cancer represent potential risk reducing options [13,14]. Women undergoing bilateral PME in the GC-HBOC program

* Corresponding author. Department of Diagnostic and Interventional Radiology, University Hospital of Cologne, Kerpener Straße 62, 50924, Cologne, Germany.
E-mail address: Barbara.krug@uk-koeln.de (B. Krug).

¹ contributed equally.

have at least one breast MRI following the surgical procedure in order to ensure that there is no relevant residual glandular tissue (RGT) remaining warranting further MRI surveillance. The nipple-areola complex (NAC) is preserved in the majority of PME for aesthetic reasons primarily, whereas in skin-sparing mastectomies, mainly carried out for curative indications, the glandular tissue and the NAC are removed leaving only the skin and a thin layer of subcutaneous fat and tissue to maintain vascularization [15,16]. The results published to date show a significant risk reduction for breast cancer in PME using different surgical techniques in the high-risk group of *BRCA1* and *BRCA2* mutation carriers [17–19]. Contralateral PME after unilateral breast cancer has also been associated with a significant risk reduction for metachronous breast cancer [13,18]. Contrarily, the analysis of breast cancer mortality rates did not indicate a benefit after PME compared to women who had not undergone PME [13,18]. Initial data published by Heemskerk-Gerritsen BAM et al., in 2015 suggest a survival benefit after contralateral PME [13]. There is currently a lack of long-term studies, which provide a sound evaluation of oncological safety concerning PME.

The risk of developing breast cancer after PME is influenced significantly by the remaining RGT. Currently, there exist only few data on the detection rates of RGT with predominantly histopathological approaches, small patient numbers ranging between 27 and 90 patients and detection rates of RGT between 5% and 61% [20–23].

The aims of this study were

- to describe frequency, localization and volume of RGT after bilateral PME, unilateral PME and curative mastectomy using breast MRI,
- to define risk constellations, in which RGT must be expected more frequently and
- to analyze the occurrence of primary breast cancer after PME during clinical follow-up.

2. Materials and methods

2.1. Inclusion and exclusion criteria

The study protocol was approved by the Local Ethics Committee. All participants of the university's Center for Hereditary Breast and Ovarian Cancer Cologne (CHBOC) who underwent unilateral or bilateral PME and received at least one postoperative breast MRI for proof or exclusion of RGT at the Radiology Department of the University Hospital of Cologne, Germany, from January 1st 2006 to December 31st 2016 were included in the study. We excluded all participants

- who had breast MRI's at other centers of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC),
- without a postoperative breast MRI,
- whose postoperative breast MRI was performed at another clinical site
- without pathogenic *BRCA1/2* germline mutation.

2.2. Patient and examination characteristics

The patient data, as well as the genomic and clinical data, were obtained from the electronic register of the CHBOC, the Hospital-Information-System (HIS) (ORBIS® OpenMed, AGFA HealthCare, NV, Mortsel, Belgium) and the Radiology-Information-System (RIS-Nice®, AGFA HealthCare, NV, Mortsel, Belgium) of the University Hospital. Two radiologists (OG, BK) checked the registries and HIS-/RIS-recordings in reference to the patient's clinical status (bilateral vs. unilateral PME). In the case of a unilateral PME, the status of the contralateral breast was recorded (curative mastectomy vs. breast conserving therapy). Concurrently, it was noted whether and, if so, at what time before and/or after the mastectomy a breast MRI was performed in the University Hospital. The last breast MRI performed before the

mastectomy and the first one after were included in the evaluations. The image documentation and follow-up were taken from the Picture Archiving and Communication System (PACS) of the University Hospital (ImpaxEE®, AGFA Healthcare, NV, Mortsel, Belgium).

2.3. MR examination techniques

Between 2006 and 2014, breast MRIs were performed using an open whole-body MRI scanner of 1.0 T main magnetic field strength (Panorama 1.0, Philips Healthcare, Best, The Netherlands) and using a whole-body MRI scanner of 1.5 T main magnetic field strength (Achieva 1.5, Philips Healthcare) with dedicated 4-channel and 7-channel breast coils. Since 2015 all breast MRIs have been acquired using whole-body MRI scanners of 1.5 T or 3.0 T magnetic field strength (Ingenia 1.5 and Ingenia 3.0, Philips Healthcare) with 16-channel breast coils. In addition, diffusion imaging was introduced into the standard protocol in 2015.

Gadoteric acid (Dotarem®, Guerbet GmbH, Sulzbach/Taunus, Germany) was used as intravenous contrast agent in a weight-adapted dose of 0.2 ml/kg body weight in all examinations. The T2-weighted sequences were used in axial orientation to determine RGT and skin flap thickness. The dynamic, contrast-enhanced 3D T1-weighted scan was acquired at six time points up until 2015 and thereafter only at points 0, 30 s, 120 s and 210 s after injection of contrast agent bolus.

2.4. Image analysis

The retrospective evaluation of the breast MRI-image data was performed at a dedicated RIS-PACS workstation (ImpaxEE®, AGFA Healthcare). As a first step, two radiologists (OG, BK) evaluated the electronic image data regarding the presence of RGT and other post-operative changes independently from each other using an electronic questionnaire. In the case of RGT localization, MRI tissue characteristics such as ACR-grade and parenchymal background enhancement were recorded. Postoperative changes such as scars, liponecrosis and seromas were also noted. The thickness of the subcutaneous tissue was measured bilaterally at two opposing sites (3 o'clock and 9 o'clock, respectively).

As a second step conflicting classifications were discussed between the two readers and a consensus was found.

As a third step the maximum sagittal (a), transverse (b) and coronal (c) diameters of RGT in a Cartesian system were independently assessed by three radiologists (BK, OG, FS). The RGT volume (V) then was extrapolated using the geometric formula of an ellipsoid ($V = 4/3\pi abc$).

As a fourth step, the RGT volume was calculated semi-automatically using special software (Intellispace®, Philips Healthcare) by three evaluators (KA, BK, OG). The results of the two volumetric techniques were collected using a structured electronic questionnaire (Excel®, Microsoft Corp., Redmond, WA, USA).

2.5. Statistical analysis

The evaluators' assessments were documented in a customized spreadsheet (Excel®, Microsoft Corp., Redmond, WA, USA). Quantitative variables were summarized by median and interquartile range (IQR, 25th to 75th percentile), qualitative variables by absolute and relative frequency (%). Bland-Altman or scatter plots were used for data illustration. Relationships were described by linear regression and Pearson's correlation coefficient. Volumes between patient subgroups were compared using the non-parametric Mann-Whitney *U* test, proportions using Fisher's exact test. In the essential exploratory analysis *p*-values < 0.05 were considered statistically significant. Calculations were carried out using SPSS Statistics software (IBM Corp., Armonk, NY, USA).

Table 1
Aggregated results classified according to the number of mastectomies carried out per surgical institution..

Number of ME per institution	Criteriu; Median (IQR) or n (%)	Prophylactic Healthy ME	Prophylactic Diseased ME	Curative ME
0–20	Breast volume prior to ME, ml	133 (70–182)	108 (93–151)	106 (106–106)
	Breast volume after ME, ml	4 (3–7)	2 (2–3)	3 (2–4)
	Width of subcutaneous tissue, mm	9 (7–13)	9 (7–14)	8 (6–13)
	Sagittal diameter of RGT, mm	3 (0–7)	0 (0–5)	0 (0–0)
	Residual retroareolar breast tissue	35/68 (51.5%)	14/39 (35.9%)	7/38 (18.4%)
	Sagittal diameter of (all) RGT: 0 mm	30/68 (44.1%)	25/39 (64.1%)	31/38 (81.6%)
	Sagittal diameter of (all) RGT: < 5 mm	9/68 (13.2%)	5/39 (12.8%)	2/38 (5.3%)
	Sagittal diameter of (all) RGT: ≥ 5 mm	29/68 (42.6%)	9/39 (23.1%)	5/38 (13.2%)
	ACR II: glandular/fatty tissue 25% - < 50%	16/38 (42.1%)	6/14 (42.9%)	4/7 (57.1%)
	ACR III: glandular/fatty tissue 50% - < 75%	22/38 (57.9%)	8/14 (57.1%)	3/7 (42.9%)
40–60	Breast volume prior to ME, ml	104 (63–140)	71 (66–93)	29 (29–29)
	Breast volume after ME, ml	4 (3–5)	2 (2–2)	1 (1–1)
	Width of subcutaneous tissue, mm	7 (5–11)	9 (5–15)	4 (3–13)
	Sagittal diameter of RGT, mm	0 (0–5)	0 (0–7)	0 (0–0)
	Residual retroareolar breast tissue	8/26 (30.8%)	5/12 (41.7%)	1/12 (8.3%)
	Sagittal diameter of (all) RGT: 0 mm	18/26 (69.2%)	7/12 (58.3%)	11/12 (91.7%)
	Sagittal diameter of (all) RGT: < 5 mm	2/26 (7.7%)	0/12 (0%)	0/12 (0%)
	Sagittal diameter of (all) RGT: ≥ 5 mm	6/26 (23.1%)	5/12 (41.7%)	1/12 (8.3%)
	ACR II: glandular/fatty tissue 25% - < 50%	6/8 (75%)	3/5 (60%)	1/1 (100%)
	ACR III: glandular/fatty tissue 50% - < 75%	2/8 (25%)	2/5 (40%)	0/1 (0%)
> 60	Breast volume prior to ME, ml	54 (40–111)	109 (53–228)	126 (61–209)
	Breast volume after ME, ml	3 (2–4)	2 (1–4)	4 (1–5)
	Width of subcutaneous tissue, mm	10 (8–17)	11 (7–14)	10 (6–13)
	Sagittal diameter of RGT, mm	3 (0–7)	0 (0–4)	0 (0–5)
	Residual retroareolar breast tissue	24/44 (54.5%)	15/48 (31.3%)	13/49 (26.5%)
	Sagittal diameter of (all) RGT: 0 mm	20/44 (45.5%)	31/49 (63.3%)	35/50 (70%)
	Sagittal diameter of (all) RGT: < 5 mm	7/44 (15.9%)	6/49 (12.2%)	3/50 (6%)
	Sagittal diameter of (all) RGT: ≥ 5 mm	17/44 (38.6%)	12/49 (24.5%)	12/50 (24%)
	ACR I: glandular/fatty tissue < 25%	0/24 (0%)	2/18 (11.1%)	0/15 (0%)
	ACR II: glandular/fatty tissue 25% - < 50%	16/24 (66.7%)	6/18 (33.3%)	3/15 (20%)
total	ACR III: glandular/fatty tissue 50% - < 75%	8/24 (33.3%)	10/18 (55.6%)	12/15 (80%)
	Breast volume prior to ME, ml	92 (55–172)	93 (65–151)	124 (61–155)
	Breast volume after ME, ml	3 (3–6)	2 (2–3)	3 (1–5)
	Width of subcutaneous tissue, mm	9 (7–13)	10 (7–14)	9 (5–13)
	Sagittal diameter of RGT, mm	2 (0–7)	0 (0–5)	0 (0–0)
	Residual retroareolar breast tissue	67/138 (48.6%)	34/99 (34.3%)	21/99 (21.2%)
	Sagittal diameter of (all) RGT: 0 mm	68/138 (49.3%)	63/100 (63%)	77/100 (77%)
	Sagittal diameter of (all) RGT: < 5 mm	18/138 (13%)	11/100 (11%)	5/100 (5%)
	Sagittal diameter of (all) RGT: ≥ 5 mm	52/138 (37.7%)	26/100 (26%)	18/100 (18%)
	ACR I: glandular/fatty tissue < 25%	0/70 (0%)	1/37 (2.7%)	0/23 (0%)
ACR II: glandular/fatty tissue 25% - < 50%	38/70 (54.3%)	15/37 (40.5%)	8/23 (34.8%)	
ACR III: glandular/fatty tissue 50% - < 75%	32/70 (45.7%)	20/37 (54.1%)	15/23 (65.2%)	

Abbreviations: ME 'mastectomy' RGT 'residual glandular tissue' IQR 'interquartile range (25th to 75th percentile)'.

3. Results

3.1. Study group

169 women met the inclusion criteria and did not fall under any of the exclusion criteria (Table 1, supplementary data). Thus, the evaluations were based on 338 MR-tomographically examined breasts in 169 women with *BRCA1/2* mutations. The median age of the 69 patients included with bilateral PME was 38.3 years ± 8.9 years standard deviation (minimum 21.2 years, maximum 58.6 years) and 42.3 years ± 8.4 years standard deviation (minimum 21.5 years, maximum 62.4 years) for the 100 patients with unilateral PME. All 100 patients with unilateral PME (100%) had either an immediate or a delayed curative mastectomy. The mastectomized breasts were analyzed separately and subdivided into the following subgroups:

1. Subgroup A: bilateral PME in healthy mutation carriers (138 breasts in 69 patients)
2. Subgroup B: unilateral PME of the healthy breast in mutation carriers with contralateral breast cancer (100 breasts in 100 patients)
3. Subgroup C: curative mastectomy of the diseased breasts (100 breasts in 100 patients).

3.2. Surgical units

The 262 mastectomies were performed in 41 hospitals. Concerning 76 mastectomies the surgical center was not apparent from the available registers. The units were divided into three groups: 0–20 mastectomies per unit, 40–60 mastectomies per unit, > 60 mastectomies per unit. The subgroup analyses showed a significantly higher RGT volume following mastectomies in the surgical units with 0–20 mastectomies compared to those with ≥ 40 mastectomies ($p < 0.033$). The proportion of RGT present following bilateral PME (subgroup A) and curative mastectomy (subgroup C) was also higher in less frequented units (0–20 mastectomies/unit versus 40–60 mastectomies/unit): subgroup A 51.5% versus 30.8%, subgroup B 35.9% versus 41.7%, subgroup C 18.4% versus 8.3% (Table 1).

3.3. Surgical techniques

According to the data of the CHBOC register, of the 338 breasts operated on (169 women), 283 breasts (83.8%) underwent skin or nipple-sparing mastectomy and 41 breasts (12.1%) underwent modified standard mastectomy, namely removal of the breast and nipple, 31 of which had secondary breast reconstruction and 10 did not. In 14 breasts (4.1%), it was unclear whether the surgical method was skin/nipple sparing or standard mastectomy with no reconstruction due to the

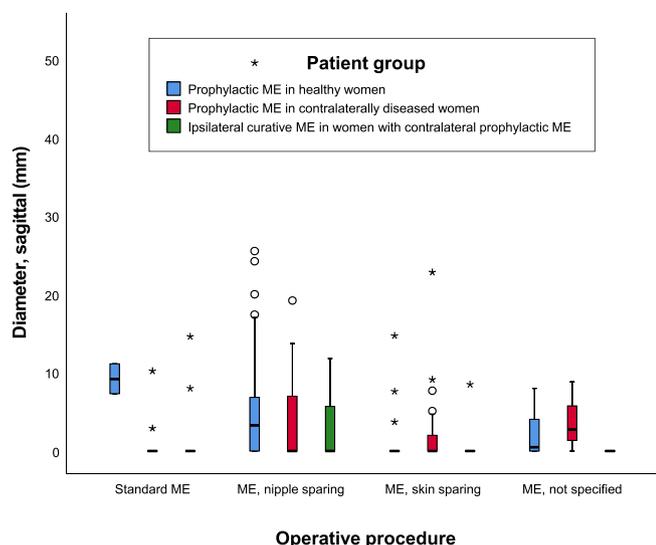


Fig. 1. Graphical representation of the depth of RGT in the sagittal “areola to thoracic wall” plane depending on the surgical technique used in bilateral PME (subgroup A), unilateral PME in contralaterally diseased women (subgroup B) and curative mastectomies in women with contralateral PME (subgroup C). Circle = statistical outlier, asterisk = numeric extreme value.

retrospective methodological approach and the inclusion of 41 breast units which implemented different documentation standards.

In subgroup A (bilateral PME) nipple sparing mastectomies were performed in 108 (78.3%) and skin sparing mastectomies were carried out in 18 (13.0%) of 136 cases. Concerning eight breasts the surgical technique was specified as either nipple sparing or skin-sparing (Fig. 1, supplementary data). Two breasts underwent standard mastectomy without reconstruction (1.4%). In two cases, no information was given on the surgical technique. In subgroup B (unilateral PME) 16 out of 100 breasts (16.0%) and in subgroup C (unilateral curative mastectomy) 23 out of 100 breasts (23.0%) had a standard mastectomy without reconstruction. 53 of the 100 unilateral PMEs (53.0%) and 46 of the 100 curative mastectomies (46.0%) were performed using nipple sparing technique. There were 22 skin sparing mastectomies (22.0%) and three mastectomies (3.0%) without further specification in subgroup B and subgroup C, respectively. In six cases the CHBOC register did not provide any information on the surgical technique used.

3.4. vol calculation techniques

Fig. 2 shows the results of the manually performed volume calculations by Cartesian determinations of the maximum diameter (step 3) compared with the results of the semi-automatic software-based calculations (step 4) in the form of a Bland-Altman-Plot. For the software-based method an above-average standard deviation towards larger volumes was found compared to the volumetric method. In the following, the software-based volumetric results were used.

3.5. Frequency of RGT

Overall, RGT was detected in 128 of the 338 breasts following mastectomy (37.9%). 68 of the 128 breasts (53.1%) were related to bilateral PME (subgroup A), 37 breasts (28.9%) to unilateral PME (subgroup B) and 23 (18%) to curative mastectomy (subgroup C). RGT appeared significantly more often after bilateral PME than unilateral PME ($p < 0.0001$). The comparison of subgroup A and subgroup C did not show a statistically significant difference ($p < 0.102$), neither did the comparison of subgroup B and subgroup C ($p < 0.199$), which may have been due to the low number of cases (Table 1).

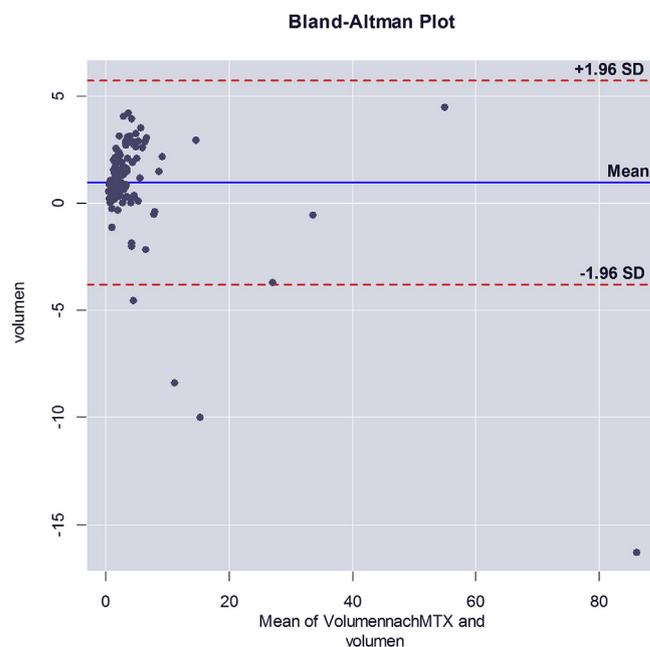


Fig. 2. Bland-Altman plot comparing the volumetric (software-based) and Cartesian (diameter-based) determinations of RGT in 128 breasts. The abscissa represents the mean of both determinations per breast and the ordinate represents the difference between the two determinations. It shows limits of agreement of -3.8 to 5.7 (ml) with bias of 0.95 (95% CI 0.53 to 1.38 , $p < 0.001$) towards larger volumes for the software-based method compared to the volumetric method.

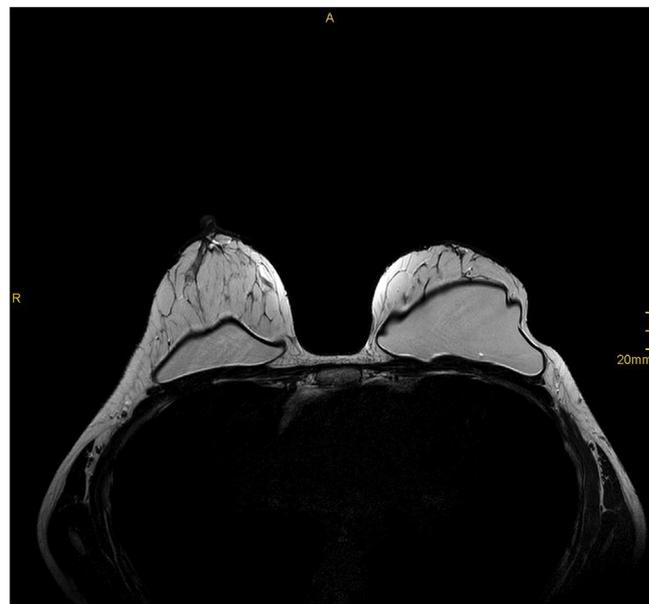


Fig. 3. Statistical outlier: 38 year-old patient who had undergone bilateral PME for a pathogen *BRCA1/2* germline mutation and bilateral reconstruction with silicone prostheses in 2013. Breast volume measured 83 ml (right side) and 105 ml (left side) preoperatively and 78 ml (right side) and 57 ml (left side) post PME.

3.5.1. RGT volume before and after mastectomy

The postoperative volumes in subgroup A averaged 3 ml (minimum 3 ml, maximum 6 ml), in subgroup B 2 ml (2 ml, 3 ml), in subgroup C 3 ml (1 ml, 5 ml) (Fig. 3). In 79 of the 128 breasts with RGT preoperative MRI scans were available. The results of a patient with average preoperative volumes (right breast 83 ml, left breast 105 ml) and postoperative RGT volumes of 78 ml on the right side and 57 ml on

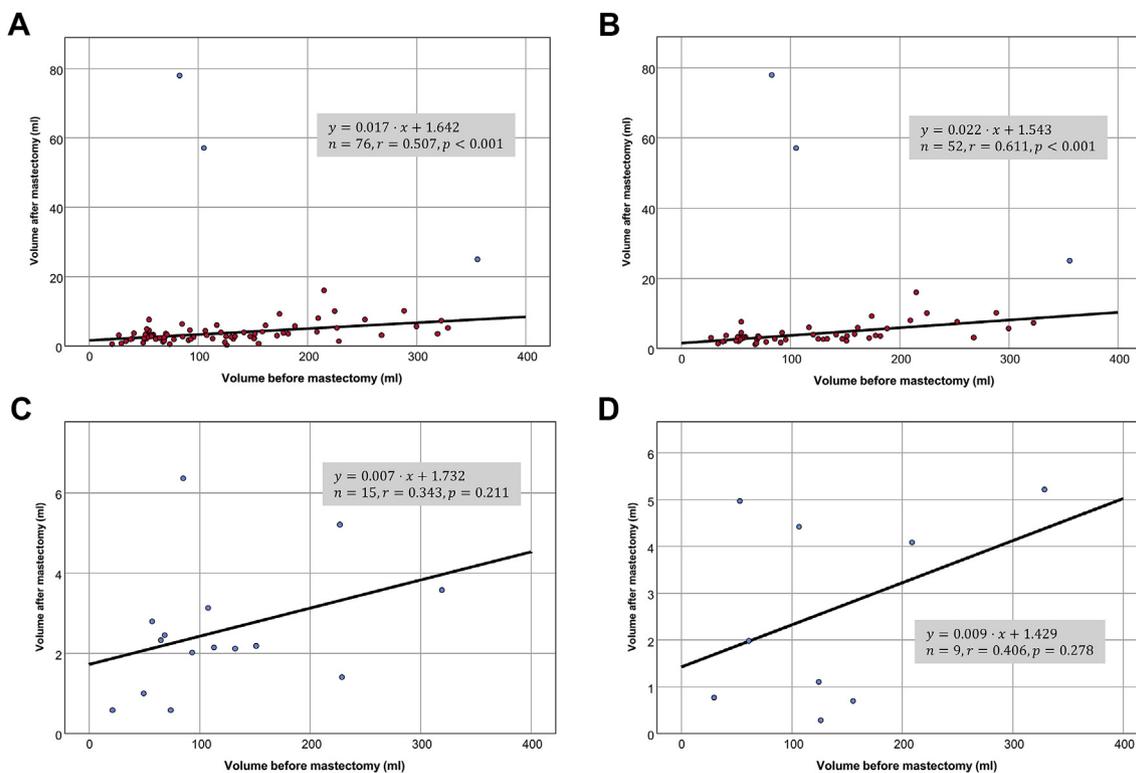


Fig. 4. Graphical representation of the volume of preoperative breast tissue on the abscissa and the RGT after mastectomy on the ordinate per breast (red dots) in patients with both preoperative and postoperative breast MRI. A positive correlation is shown between preoperative breast volume and RGT volume when considering all 76 breasts (Fig. 4A), the subgroup of bilateral PME (Fig. 4B), the subgroup with unilateral PME (Fig. 4C) and the subgroup with curative mastectomy (Fig 4D) ($p < 0.001$). Three outliers with RGT of 78 ml, 57 ml and 29 ml after bilateral PME (blue dots) were excluded from statistical analysis.

- A All 76 breasts with RGT and preoperative breast MRI
- B 52 breasts with bilateral PME
- C 15 breasts with unilateral PME
- D Nine breasts with curative mastectomy.

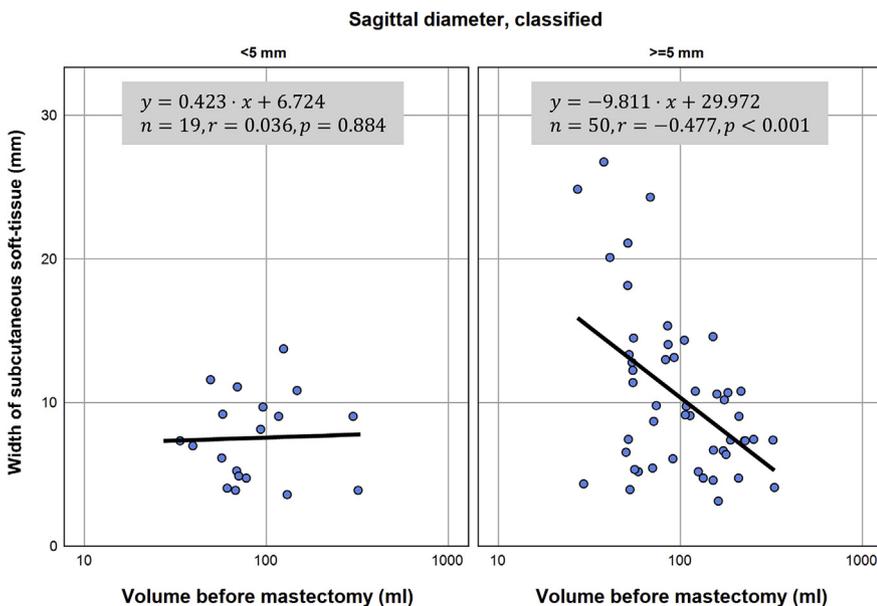


Fig. 5. Graphical representation of the width of the postoperative soft tissue on the ordinate and the preoperative gland volume on the abscissa divided into two groups: retroareolar RGT < 5 mm in the sagittal diameter (left) and ≥ 5 mm (right) demonstrating a significant reduction of soft tissue in bigger preoperative volumes in the second group (right).

left side were excluded from the statistical calculations as statistical outliers. The regression analysis confirmed a linear relationship between the RGT volume before and after mastectomy across all subgroups as well as in the independently analyzed subgroups, indicating that larger preoperative baseline volumes contain more RGT post mastectomy (Fig. 4A–D).

3.5.2. Localization of RGT

In 122 of the 128 breasts affected, the RGT was localized in the retroareolar breast region (94.6%). In subgroup A the RGT was detected in the retroareolar breast region in 67 out of 70 cases (95.7%), in subgroup B in 34 out of 36 cases (94.4%) and in subgroup C in 21 out of 23 cases (91.3%). Independent of subgroup allocation, retroareolar

RGT was most often found following nipple sparing mastectomy (Fig. 1). Multifocal RGT was an exception and concerned only seven breasts in subgroup A (10%). In subgroup B and subgroup C, there was no case of multifocal RGT.

3.5.3. Sagittal diameter of RGT

The retroareolar extension of RGT, defined as the sagittal RGT diameter measured between the areola and the thoracic wall, averaged 2 mm (minimum 0 mm, maximum 7 mm) in subgroup A, 0 mm (0 mm, 5 mm) in subgroup B and 0 mm (0 mm, 0 mm) in subgroup C. In subgroup A 52 of the 138 breasts showed RGT with a sagittal diameter of ≥ 5 mm (37.7%), in subgroup B 26 of the 100 breasts showed such a diameter (26%) and in subgroup C 18 of the 100 breasts (18%) were found to have RGT with ≥ 5 mm sagittal diameter (Table 1). A sagittal RGT diameter ≥ 5 mm showed a significant correlation between the thickness of the subcutaneous tissue and the preoperative initial volume with increasingly narrow flap at larger initial volumes (Fig. 5).

3.5.4. Thickness of the subcutaneous tissue

The mean thickness of the subcutaneous tissue was 9 mm (minimum 7 mm, maximum 13 mm) in subgroup A, 10 mm (7 mm, 14 mm) in subgroup B and 9 mm (5 mm, 13 mm) in subgroup C (Table 1). The regression analysis of RGT and the postoperative subcutaneous soft tissue showed a positive trend towards larger RGT volumes in thicker soft tissue flaps (Fig. 6). RGT in the retroareolar breast region showed a negative trend towards narrower soft-tissue flaps in breasts with larger initial volumes (Fig. 7).

3.6. Clinical follow-up

The median time to follow-up under the CHBOC program was 4.3 years (minimum six months, maximum 19 years). Breast cancers were recorded in two patients five years after bilateral PME and two years after unilateral PME respectively in locations without RGT as visualized by the index breast MRI. In the first case of retroareolar RGT, in the index-MRI, the carcinoma was located in the periphery of the left upper outer quadrant according to the clinical documentation. In the second case there was no RGT visualized in the index-MRI.

4. Discussion

In the present study, RGT was detected in 128 of 338 mastectomized breasts (37.9%). In more than 50% (68 of 128 breasts), RGT was related to bilateral PME and was present significantly more often after bilateral PME than after unilateral PME and curative mastectomy. RGT was

localized mainly in the retroareolar breast region (122 of 128 breasts) with multifocal RGT being an exception and concerning only 10% of the bilaterally mastectomized breasts (seven breasts). While 97.1% of the bilateral PME were carried out using skin or nipple-sparing technique, 16% of the unilateral PME and 23% of the curative mastectomies were carried out using standard mastectomy technique with and without reconstruction. Therefore, RGT is a common postoperative finding that appears to be related to the selected surgical technique. In accordance with the present results *Woitek et al.* evaluated postoperative MRI scans of 58 patients after prophylactic skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) and found RGT in 20% of all breasts and significantly more frequently after NSM than SSM [24]. *Van Verschuer et al.* histologically analyzed 105 Nipple-Areola-Complexes (NACs) and adjacent skin islands in 90 women after prophylactic skin-sparing (31 cases) and curative mastectomies (71 cases). They found evidence of RGT in 61% of the NAC samples and 24% of the skin samples but did not differentiate between the two surgical indications [23].

In the present study, a significantly higher RGT volume was found in breasts mastectomized in the less frequented surgical units with > 20 mastectomies compared to those with ≥ 40 mastectomies ($p < 0.033$), which indicates that the individual surgeon's expertise or the cumulative team experience has a marked impact on the clinical outcome.

For the two-point measurements (horizontal direction, 3 o'clock and 9 o'clock), the thickness of the subcutaneous tissue averaged 10.5 mm with maximum values of 52.3 mm. In accordance with our approach *Zippel et al.* used postoperative MRI to evaluate residual breast tissue in 88 breasts after prophylactic ($n = 43$) and curative mastectomies ($n = 45$) and reconstruction using silicone prostheses at four points with similarly high mean and maximum values (mean 11.2 mm, maximum 53.4 mm) [25]. Additionally, there was an association between the thickness of the subcutaneous tissue and RGT volume, especially at locations other than the retroareolar breast region. These findings are concordant with the histological results of *Torresan et al.* who showed a significant association ($p < 0.005$) between the presence of RGT and skin flap thickness of more than 5 mm [22].

The sagittal diameter of retroareolar RGT was ≥ 5 mm in 96 of the 130 mastectomized breasts (74%) and thus exceeded the recommended 5 mm limit for the maintenance of subdermal vascularization [26,27]. The mean and maximum diameters were larger after bilateral PME when compared with unilateral PME and curative mastectomy. These results support the hypothesis that different surgical indications and chosen techniques influence the clinical outcome significantly. *Baltzer et al.* used breast MRI to measure the retroareolar fibroglandular tissue relative to the entire glandular body at 5 mm and 10 mm retroareolar diameters on a total of 105 *BRCA1/2* mutation carriers [28]. The proportion of retroareolar glandular tissue assuming a sagittal diameter of 5 mm averaged only 1.3% of the total glandular tissue. However, increasing the diameter to 1 cm showed a highly significant increase of the proportion to 3% ($p < 0.001$). Even a proportion of 1.3% appears clinically relevant taking into account the fact that both carcinomas we detected during the follow-up appeared as microscopically undetectable RGT.

The median time to follow-up was 4.3 years (minimum 6 months and maximum 19 years). Two out of 169 women developed breast cancer following PME after two and five years, respectively. Despite the use of nipple-sparing technique (78.3% in subgroup A), no carcinoma was observed in the retroareolar breast region. This is in accordance with the results of the multi-center study by *Orzalesi et al.* who found following 1006 nipple-sparing mastectomies (12.3% PME), recurrence of cancer in the NAC in 0.7% over a mean follow-up period of 1101 days [29]. *Yao et al.* analyzed 397 nipple-sparing mastectomies in *BRCA1/2* mutation carriers (74.6% PME) with a total of four breast cancers (one carcinoma after PME) on average in the follow-up period of 32.6 months, with no NAC involvement [30]. *Manning et al.* did not record any oncological events after a total of 177 nipple-sparing

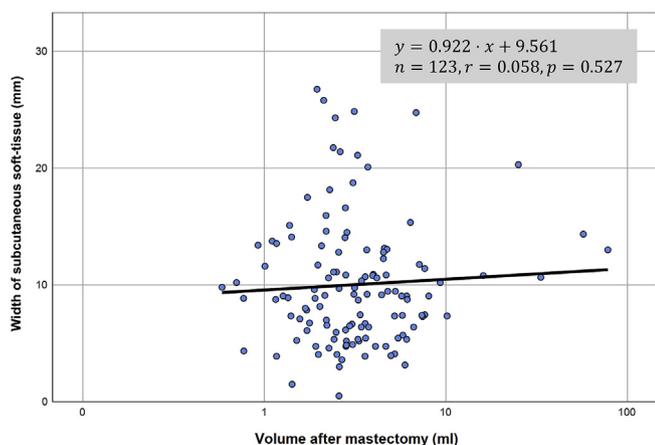


Fig. 6. Correlation of the width of the postoperative soft tissue (plotted on the ordinate) and the postoperative RGT (plotted on the abscissa), including all three subgroups demonstrating a positive trend.

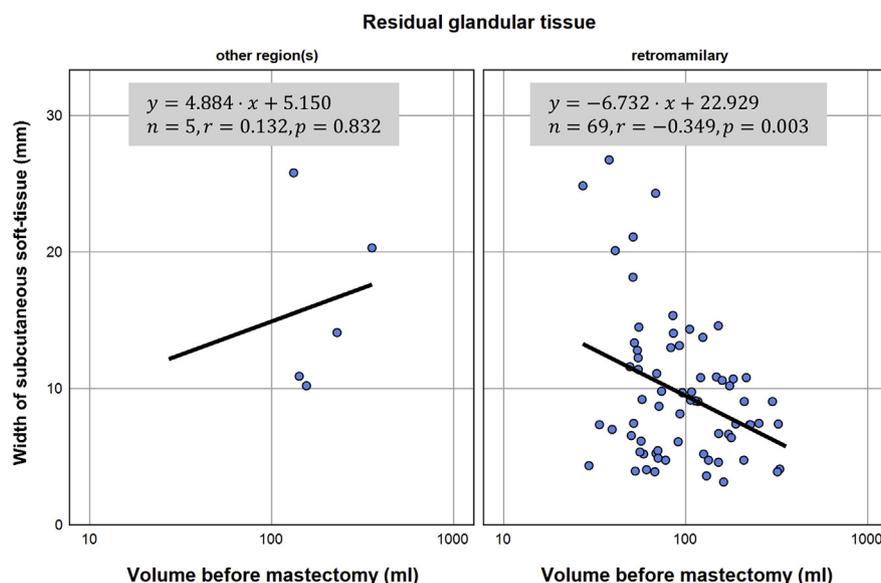


Fig. 7. Comparison of the thickness of the postoperative soft tissue (ordinate) and the preoperative gland volume (abscissa) divided into two groups: RGT localization other than in retroareolar breast region (left) and RGT in the retroareolar breast region (right) demonstrating a negative trend in the second group.

mastectomies in *BRCA 1/2* mutation carriers during an average follow-up period of 2.15 years [31]. However, the short follow-up period is indeed a mentionable limitation of these studies. Hartmann et al. followed-up 639 women at increased hereditary risk for breast cancer, who underwent PME, for a median of 14 years [32]. Seven of these women developed breast cancer 2–25 years after mastectomy, only one of them in the NAC. Skytte et al. surveyed 307 healthy *BRCA1/2* mutation carriers; 96 of them having undergone bilateral PME [33]. Three of them developed breast cancer at intervals of two, five and seven years after PME. Two of the carcinomas were located on the thoracic wall and one in the axilla. Based on those results, the working group calculated a cumulative ten-year incidence for the cohort of mastectomized mutation carriers of about 10%. Since no image correlation took place in these studies, it prompts the question about underlying RGT.

The present study has the following methodological limitations:

- Long-term follow-up was only possible in a subgroup of patients, because quite a number of women left the screening program after the first postoperative follow-up and/or because the time interval between mastectomy and the evaluations was rather short. Some oncological events might have been missed for this reason.
- The volume measurements of RGT were hampered by the fact that in particularly fatty breasts and in breasts with only scattered areas of fibroglandular density, the exact discrimination of glandular tissue, subcutaneous septae and postoperative scars was difficult. Due to the limited spatial resolution of breast MRI, small glandular bonds at cellular level, which may be the origin of breast cancer, cannot be visualized by breast MRI. Further prospective studies are warranted in order to answer the question as to whether long-term MRI surveillance in women with an increased risk of breast cancer following bilateral PME is advisable.

5. Conclusions

RGT is a common finding after PME and curative mastectomy that varies depending on the surgical indication and the chosen surgical procedure in individual patients. In particular, the selected surgical procedure (standard mastectomy with and without reconstruction versus skin-sparing mastectomy) affects both the incidence and the extent of postoperative RGT. Moreover, the surgeon's and the patient's preferences for balanced aesthetic results seem to influence the surgical

outcome. In view of these findings, radiologists should report on RGT more consistently and the continuation of structured image-based surveillance of *BRCA1/2* mutation carriers has to be discussed even following PME if RGT persists. However, large-scale, prospective, long-term studies are needed in order to assess the oncological risk associated with RGT and to define the role of breast MRI in the management of patients following PME.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.suronc.2019.04.009>.

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