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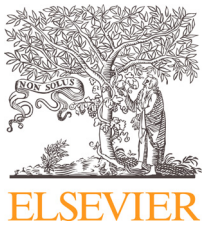

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Prophylactic mastectomy – Correlation between skin flap thickness and residual glandular tissue evaluated postoperatively by imaging

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Summary *Background:* Women with an increased hereditary risk of breast cancer can undergo risk-reducing prophylactic mastectomy. However, there is a balance between how much subcutaneous tissue should be resected to achieve maximal reduction of glandular tissue, while leaving viable skin flaps.
Methods: Forty-five women previously operated with prophylactic mastectomy underwent magnetic resonance tomography (MRT) and ultrasound (US) to investigate the correlation between skin flap thickness and residual glandular tissue. Residual glandular tissue was documented as being present or not present, but not quantified, as the amount of residual glandular tissue in many cases was considered too small to make reliable volume quantifications with available tools. Since a mastectomy skin flap thickness of 5 mm is discussed as an oncologically safe thickness in the literature, this was used as a cut-off.
Results: Following prophylactic mastectomy, residual glandular tissue was detected in 39.3% of all breasts and 27.9% of all the breast quadrants examined by MRT, and 44.1% of all breasts and 21.7% of all the breast quadrants examined by US. Residual glandular tissue was detected

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in 6.9% of the quadrants in skin flaps ≤ 5 mm and in 37.5% of the quadrants in skin flaps > 5 mm (OR 3.07; CI = 1.41–6.67; $p = 0.005$). Furthermore, residual glandular tissue increased significantly already when the skin flap thickness exceeded 7 mm.

Conclusions: This study highlights that complete removal of glandular breast tissue during a mastectomy is difficult and suggests that this is an unattainable goal. We demonstrate that residual glandular tissue is significantly higher in skin flaps > 5 mm in comparison to skin flaps ≤ 5 mm, and that residual glandular tissue increases significantly already when the flap thickness exceeds 7 mm.

Introduction

Breast cancer is the most common form of cancer among women.[1] Five to ten percent of all breast cancers are due to hereditary factors,[1] with pathogenic variants in the breast cancer genes BRCA1/2 accounting for 2–5% of all breast cancer.[1] Women with pathogenic variants in BRAC1/2 have a 50–80% lifetime risk of developing breast cancer,[2,3] and are therefore offered surveillance with different imaging protocols or risk-reducing prophylactic mastectomy with immediate reconstruction,[1] the latter reducing the risk of breast cancer up to 90%.[3] The survival benefits with this operation are, however, not clear.[4]

There are established surveillance guidelines for women with pathogenic variants in BRCA1/2, who do not undergo prophylactic surgery, but no published consensus or guidelines regarding appropriate medical follow-up for those who opt for prophylactic mastectomy. According to the National Comprehensive Cancer Network (NCNN) [5] women operated with risk-reducing prophylactic mastectomy should continue with annual exams of the chest/reconstructed breasts as there is still a small risk of developing breast cancer. However, they do not specify what should be included in an annual exam, other that mammograms are not recommended in this setting. According to the National Institute for Health and Care Excellence (NICE) in the United Kingdom,[6] one should not offer surveillance to women who have undergone prophylactic bilateral mastectomy. Some studies imply that a physical examination should be done at least annually,[7] while others claim that the risk for cancer is too low to justify any type of surveillance.[8,9] The number of studies investigating the use of magnetic resonance tomography (MRT), ultrasound (US) and mammography after prophylactic mastectomy with reconstruction is limited, and among clinicians, the opinion differs on whether imaging has a role in the follow-up of this patient group.[7]

Among women who have undergone prophylactic mastectomy, 1–1.9% are diagnosed with breast cancer,[3] but little is known about the correlation between residual glandular tissue and skin flap thickness, as well as the oncological risk of residual glandular tissue. Based on both histological and imaging-based studies, some authors propose that the skin flap thickness should not exceed 5 mm, due to a significant increase in residual glandular tissue.[10,11] However, a major clinical problem with very thin skin flaps is that it becomes difficult to maintain a viable circulation, with skin flap necrosis present in 30% of patients with 4–5 mm thick skin flaps.[12,13]

The aim of this study was to investigate the correlation between skin flap thickness and residual glandular tissue following prophylactic mastectomy using postoperative MRT and US investigations. Since a mastectomy skin flap thickness of 5 mm is discussed as an oncologically safe thickness in the literature, this was used as a cut-off.

Material and methods

Women with elevated risk of developing breast cancer due to hereditary factors operated with prophylactic mastectomy at the Department of Plastic surgery at Umeå University Hospital between 1997 and 2016 were invited to participate in the study.

In total, 73 women were invited to the study. Twenty-seven of these women declined and one woman with very high body mass index (BMI) was excluded because she could not be examined with MRT. Breasts mastectomized due to cancer and those reconstructed with autologous tissue were furthermore excluded.

All included women underwent MRT and US at the same timepoint. The thickness of the skin flaps and any residual glandular tissue in each breast quadrant were documented in a standardized manner in a pre-printed clinical report form. Each breast analysed was divided into four quadrants, i.e. the inner lower, the inner upper, the outer lower and outer upper quadrant, and thus, a total of 284 available measuring points were obtained.

The skin flap thickness is defined as the thickness of the skin (epidermis, dermis, and subcutaneous tissue) measured at the examinations rather than the thickness of the skin flaps perioperatively. To obtain the mean skin flap thickness in each breast, the skin flap thickness in the four quadrants were added together and divided by four. All measurements were made in mm. US was used as the method to measure skin flap thickness since we demonstrated in a previous publication that US seemed to be a more accurate method for measuring skin flap thickness in comparison to MRT.[13] Residual glandular tissue was documented as being present or not present in each quadrant, but not quantified. The breast radiologists analysed the electronic MRT and US images visually. Regarding the MRT, a full MRT protocol, consisting

of STIR, T1W TSE, eTHRIVE with and without intravenous contrast and T2W TSE with intravenous contrast, was performed, and all sequences were therefore used for detection of glandular tissue. Following contrast administration, dynamic sequences were acquired at five timepoints and an axial plane of acquisition was used. Two different radiologists interpreted the MRT and US examinations, dividing half of the examinations between them.

Ethics

The study was performed according to the principles of the declaration of Helsinki and ethical guidelines of the Swedish research council. Ethical approval was obtained from the regional vetting board in Umeå (Dnr 2017–141-31 M, 20,170,530). All participating patients gave informed written consent.

Statistics

Patient characteristics and frequencies of events were summarized using descriptive statistical methods. To measure the inter-rater agreement between the imaging methods in detecting residual glandular tissue, Cohen's kappa coefficient was used. To handle the repeated measurements within each patient a generalized estimating equations (GEE) model with binary logistic link was used to assess the difference in residual glandular tissue between different breast quadrants and breast side and to analyze the correlation between residual glandular tissue and different skin flap thicknesses. In the GEE model, an exchangeable covariance structure was used. Data analyses were performed by SPSS statistical software (IBM SPSS 22). Test results with p-values of less than 0.05 were considered statistically significant.

Results

Study population

Forty-five women met the inclusion criteria, rendering 70 mastectomized breasts reconstructed with implants or not reconstructed to be included in the analysis (Supplementary Fig. 1). Mean age at prophylactic mastectomy was 43.3 (±10.4) years and mean time between prophylactic mastectomy and follow-up was 8.0 (±5.5) years. Of these 45 women, 21 underwent bilateral prophylactic mastectomy without a previous cancer, 16 underwent contralateral prophylactic mastectomy and eight underwent bilateral prophylactic mastectomy after a previous cancer operated on using breast conserving surgery. All breasts were operated with some kind of skin sparing mastectomy (SSM); 41/70 breasts were operated with SSM, 27/70 breasts were operated with nipple sparing mastectomy and 2/70 breasts were operated with SSM with nipple transplantation. Out of the 70 included breasts, 67 breasts were reconstructed with implants and three breasts were not reconstructed at all. The three unreconstructed breasts were operated with SSM instead of simple mastectomy since the intention was to perform the reconstruction in a later stage. Following reconstruction with implants, a large proportion of the patients, 31/67, underwent additional surgeries for several reasons, including implant loss due to infection/necrosis, implant exchange due to a two stage reconstruction with change from an expander to a permanent implant, implant exchange due to change of location or size of the implant without clinical signs of capsular contracture, capsular contractures, autologous fat transplantation and revision of scar. Clinical characteristics and treatment modalities for all patients are presented in Table 1. The cohort is described in detail in a previous paper.[13] Following prophylactic mastectomy, no women got breast cancer in the ipsilateral breast. Out of these 45 women, five did not undergo MRT and two did not undergo US. One woman did not undergo MRT due to claustrophobia, one woman due to implants containing metal, two women refused MRT as they recently had performed a breast MRT at another hospital, and were thus

Table 1 Clinical characteristics and surgical history. Clinical characteristics and surgical history in 45 women and 90 breasts.

	%
Age at prophylactic mastectomy, years Mean (SD)	43.3 (±10.4)
Time between prophylactic mastectomy and follow-up, years Mean (SD)	8.0 (±5.5)
Surgical history	
Prophylactic bilateral mastectomy without previous cancer	46.7 (21/45)
Prophylactic contralateral mastectomy	35.6 (16/45)
Prophylactic bilateral mastectomy due to previous cancer operated with breast conserving therapy	17.8 (8/45)
Surgical technique	
Skin sparing mastectomy	58.6 (41/70)
Nipple sparing mastectomy	38.6 (27/70)
Skin sparing mastectomy with nipple transplantation	2.9 (2/70)
Reconstruction	
Implant	95.7 (67/70)
Not reconstructed at all	4.3 (3/70)
Additional surgery after reconstruction with implants	46.3 (31/67)
Additional surgery regardless of etiology	53.7 (36/67)
Yes	28.4 (19/67)
No	7.5 (5/67)
Implant exchange regardless of etiology	14.9 (10/67)
Implant loss due to infection/necrosis	6.0 (4/67)
Capsular contracture requiring surgery	
Autologous fat transplantation	
BMI preoperatively	
Mean (SD)	25.0 (±3.9)
BMI at follow-up	
Mean (SD)	26.1 (±4.3)

unwilling to undergo the same procedure again and finally one woman because she could not fit into the MRT machine due to high BMI. The protocol used for breast MRT at the other hospital differed too much from that performed at our unit to allow for inclusion of these images into the present analysis. US was not performed in one woman because she had two weeks previously undergone surgery due to a spontaneous hematoma of the breast with implant removal and hematoma evacuation, making it difficult to interpret the results, and one woman did not undergo US due to implant rupture, also complicating the interpretation of the imaging.

Residual glandular tissue

Presence of residual glandular tissue following prophylactic mastectomy was investigated with MRT ($n = 61$ breasts and $n = 244$ quadrants) and US ($n = 68$ breasts and $n = 272$ quadrants). The number of quadrants with residual glandular tissue is expressed in percentage of the total number of examined quadrants. Following prophylactic mastectomy, residual glandular tissue was detected in 39.3% of all breasts and 27.9% of the breast quadrants examined by MRT, and 44.1% of all breasts and 21.7% of the breast quadrants examined by US.

The inter-rater reliability kappa statistic between MRT and US in detecting residual glandular tissue following prophylactic mastectomy was 0.571, considered as moderate agreement.

Distribution of residual glandular tissue

The distribution of residual glandular tissue between breast quadrants and breast side was assessed. Residual glandular tissue was detected with MRT in 21.3% of the upper inner quadrants, in 34.4% of the lower inner quadrants, in 29.5% of the lower outer quadrants and in 26.2% of the upper outer quadrants, with significantly more residual glandular tissue detected in the lower inner quadrants in comparison to the upper inner quadrants ($p = 0.002$) and between the lower inner quadrants in comparison to the upper outer quadrants ($p = 0.012$) (Figure 1A). The distribution of residual glandular tissue did not differ significantly between the right and left breast ($p = 0.833$). Residual glandular tissue was detected with US in 16.2% of the upper inner quadrants, in 29.4% of the lower inner quadrants, in 25.0% of the lower outer quadrants and in 16.2% of the upper outer quadrants, with no significant difference in detection of glandular tissue between the four different quadrants ($p = 0.073$) (Figure 1B), nor between the right and left breast ($p = 0.452$).

Correlation between residual glandular tissue and skin flap thickness

Correlation between residual glandular tissue measured with MRT and skin flap thickness measured with US was analysed in two different groups, skin flaps $\leq$ 5 mm ($n = 72$ quadrants) and skin flaps $>$ 5 mm ($n = 168$ quadrants)

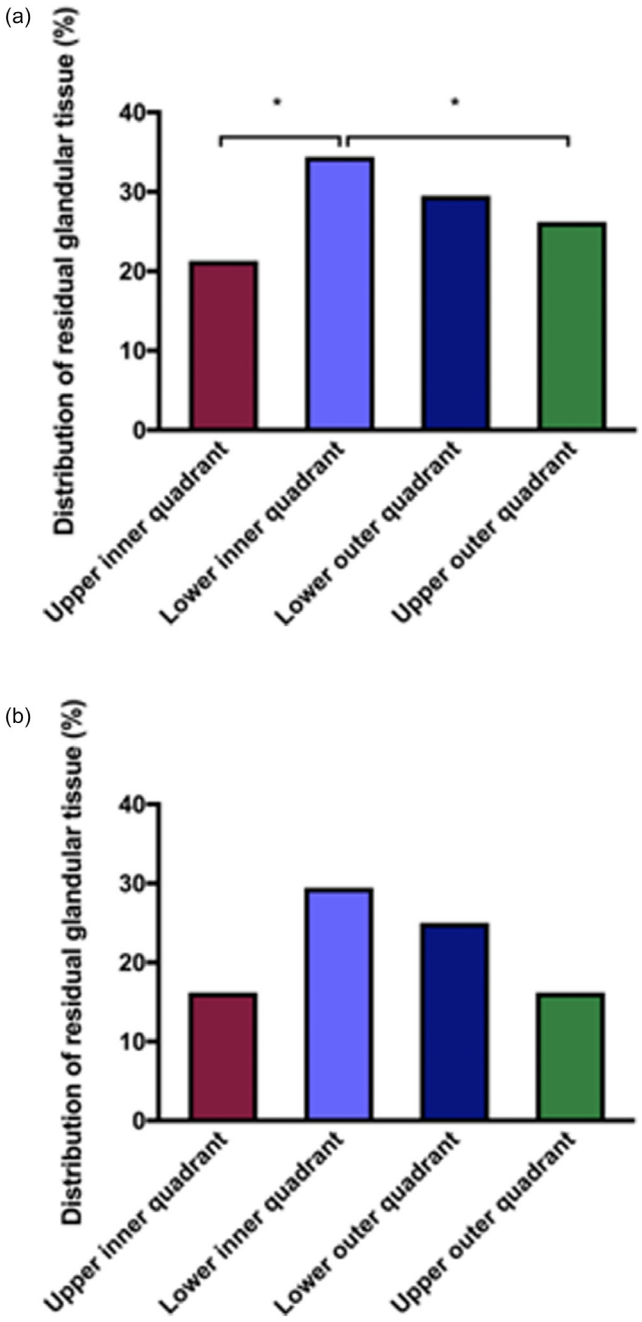

Figure. 1 Distribution of residual glandular tissue. The distribution of residual glandular tissue in the upper inner quadrant, lower inner quadrant, lower outer quadrant and upper outer quadrant following prophylactic mastectomy was investigated by A) magnetic resonance tomography and B) ultrasound. A generalized estimating equation model with binary logistic link was used to assess the difference in estimated residual glandular tissue between the different breast quadrants. Test results with a p-value of less than 0.05 (*) were considered statistically significant.

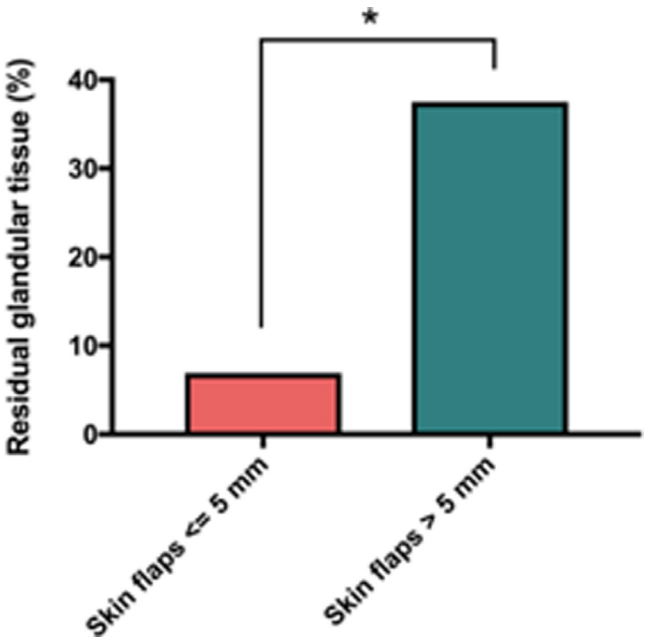

Figure. 2 Correlation between residual glandular tissue and different skin flap thickness. Correlation between residual glandular tissue measured with magnetic resonance tomography and skin flap thickness measured with ultrasound in two different groups, skin flaps $\leq$ 5 mm ($n = 72$ quadrants) and skin flaps $>$ 5 mm ($n = 168$ quadrants), was calculated with a generalized estimating equation model with binary logistic link. Test results with a p-value of less than 0.05 (*) were considered statistically significant.

(Figure 2.). Following prophylactic mastectomy, residual glandular tissue was detected in 6.9% of the quadrants in skin flaps $\leq$ 5 mm and in 37.5% of the quadrants in skin flaps $>$ 5 mm (OR 3.07; CI 1.41-6.67; $p = 0.005$). Thus, the amount of residual glandular tissue increased significantly with increased skin flap thickness.

Correlation between residual glandular tissue per unit of increased skin flap thickness

The correlation between residual glandular tissue per unit of increased skin flap thickness (measured in millimetres) was assessed, with skin flaps $\leq$ 5 mm used as a control (Table 2). No significant difference in the amount of residual glandular tissue was seen between skin flaps $\leq$ 5 mm and skin flaps 5.1-6 mm (OR = 2.53; CI = 0.93-6.91; $p = 0.070$), nor between skin flaps $\leq$ 5 mm and 6.1-7 mm (OR = 1.68; CI = 0.58-4.88; $p = 0.340$). However, when the skin flap thickness exceeded 7 mm, the amount of residual glandular tissue increased significantly, with increased glandular tissue observed in all skin flap groups thicker than 7 mm in comparison to skin flaps $\leq$ 5 mm (Table 2).

Discussion

To date, little is known about the prevalence and localization of residual glandular tissue after mastectomy. It is established that a small proportion of glandular tissue can remain, but the percentage of patients in whom this is found varies between different studies, with residual glandular tissue being reported in 5 to 76% of all breast specimens in histopathological reports [14,15] and in 20-40% of all women in imaging-based studies.[16,17] Griepsma et al.[15] investigated the prevalence and localization of residual glandular tissue after a mastectomy in 206 patients using histological sampling, with one or more positive biopsy samples found in 76.2% of the specimens. The positive findings were found with a significant predilection for the lower outer quadrant and the middle circle. Barton et al.,[14] on the other hand, demonstrated a much lower percentage. Multiple biopsies were taken from the anterior chest walls of women following mastectomy, with residual glandular tissue identified histologically in 5% of all biopsy specimens. We showed that residual glandular tissue was detected in 39.3% of all breasts and 27.9% of all the breast quadrants examined by MRT, and 44.1% of all breasts and 21.7% of all the breast quadrants examined by US, which is in line with other imaging-based studies.[16,17]

Although the presence of residual glandular tissue has been analysed in other imaging-based studies,[11,16-18] there are, however, very few studies that have evaluated the specificity and sensitivity of detecting residual glandular tissue with imaging, and there is often only one radiologist performing the analysis with no intra- or inter-reliability values reported.[19] The limited spatial resolution with MRT makes it hard to discriminate between glandular and fibrotic tissue why small amounts of glandular tissue could be mistaken for ligaments, scar tissue or artefacts and the other way around.[16]

So how thin should the skin flaps be to be considered oncological safe, and at the same time leave an acceptable outcome in terms of aesthetics? And if one leaves thicker skin flaps, is some kind of postoperative surveillance motivated? In regard to detection of remaining glandular tissue, we demonstrated that MRT and US showed comparable results with moderate inter-rater reliability.

Some authors propose that the skin flap thickness should not be thicker than 5 mm,[10,11] while others claim that 10 mm thick skin flaps are oncologically safe.[20-22] Torresan et al. [10] analysed the correlation between remaining glandular tissue and skin flap thickness in 42 breast cancer patients. Before surgery, two lines were drawn on the breast skin, representing skin sparing mastectomy and simple mastectomy incisions. After surgery, the skin flap that would remain after skin sparing mastectomy was removed and the presence and amount of remaining glandular breast tissues were histologically evaluated in the skin flap. Remaining glandular tissue was present in 46.2% of the skin flaps $\leq$ 5 mm and in 81.3% of the skin flaps $>$ 5 mm. Furthermore, Baltzer et al.[11] evaluated the proportion of residual glandular tissue present in the nipple areolar complex relative to the whole breast with MRT, and demonstrated that increasing the retroareolar surgical margin from 5 to 10 mm, significantly increased the proportion of residual glandular tissue. Cao et al.[23] analysed the involvement of the superficial specimen margin from 168 skin-sparing mastectomies. During surgery, a biopsy was taken from the dermis side of the skin flap directly overlying the tumor, and in a thicker skin flap biopsy (12 mm compared with 8.6 mm) signifi-

Table 2 Correlation between residual glandular tissue per mm increased skin flap thickness. Correlation between residual glandular tissue measured with magnetic resonance tomography and increased skin flap thickness measured with ultrasound was calculated with a generalized estimating equation model with binary logistic link. The difference between the different skin flap thickness groups is expressed with odds ratio (OR), with skin flaps $\leq$ 5 mm used as a control.

Skin flap thickness	*(%)*	*OR (CI)*
$\leq$ 5 mm	5/72 (6.9)	Ref
5.1–6 mm	8/30 (26.7)	2.53 (0.93–6.91; $p = 0.070$)
6.1–7 mm	4/25 (16.0)	1.68 (0.58–4.88; $p = 0.340$)
7.1–8 mm	14/29 (48.3)	5.68 (2.28–14.13; $p = 0.000$)
8.1–9 mm	11/26 (42.3)	4.94 (1.75–13.96; $p = 0.003$)
9.1–10 mm	8/21 (38.1)	3.58 (1.57–8.16; $p = 0.002$)
$\geq$ 10.1 mm	18/37 (48.6)	3.99 (1.53–10.41; $p = 0.005$)

cantly more glandular tissue was detected ($p = 0.019$). In line with above mentioned studies, we demonstrated that the amount of residual glandular tissues was much higher in thicker skin flaps; residual glandular tissue was detected in 6.9% of the breast quadrants in skin flaps $\leq$ 5 mm and in 37.5% of the quadrants in skin flaps $>$ 5 mm (OR = 3.07; CI = 1.41–6.67; $p = 0.005$). In addition, the amount of residual glandular tissue significantly increased when the skin flap thickness exceeded 7 mm in comparison to skin flaps $\leq$ 5 mm.

In contrast to what one might expect, the thickness of the subcutaneous layer between the dermis and the breast parenchyma does not seem to correlate with the BMI of the patient nor with breast sample weight.[13,20] In a previous paper, we demonstrated that neither the BMI preoperatively or the BMI change between surgery and follow-up did affect the skin flap thickness significantly.[13] Furthermore, Larson et al. [20] investigated the non-breastbearing subcutaneous tissue layer between the dermis of the breast and its parenchyma, and demonstrated that no significant correlation was found between the thickness of the subcutaneous tissue and BMI, age or breast sample weight. Neither does it seem to be a significant association between remaining glandular tissue and menopausal status or mammographic density.[10]

A major clinical problem with very thin skin flaps is however that it becomes difficult to maintain a viable circulation, with skin flap necrosis present in 30% of the patients with 4–5 mm thick skin flaps.[12] In addition, we demonstrated in an earlier study [13] that the odds of skin necrosis was more than six times higher in skin flaps $\leq$ 5 mm compared to skin flaps $>$ 5 mm. Besides the skin flap thickness, several individual factors affect the risk of skin flap necrosis, like smoking and radiotherapy.[13,24]

Our study has limitations. Twenty-seven women chose not to participate for unknown reasons, mediating a certain risk of selection bias. Furthermore, although the number of measuring points was high, the cohort of included women was small. In addition, potential confounding factors that may affect the measuring of the skin flap thickness, like earlier skin flap necrosis (12/71 breasts) and additional surgeries following reconstruction with implants (31/67) has not been addressed in the analysis of the data due to the small cohort. The strengths are the design with all women undergoing MRT and US at the same timepoint, which renders the cohort suitable to comparative studies of this methods.

In conclusion, our study highlights the difficulty of achieving complete removal of all breast tissue when performing a mastectomy and suggests that this is an unattainable goal. From what we demonstrate here, one could thus argue that the skin flap thickness should not exceeded 7 mm. However, the variable and unpredictable thickness of the breast subcutaneous layer between patients, individual risk factors like smoking and radiotherapy, as well as the unknown oncological risk with residual glandular tissue, makes recommendations regarding a specific universal thickness for mastectomy skin flaps difficult.

Declaration of Competing Interest

None of the authors has a financial interest in any of the products, devices or drugs mentioned in this manuscript.

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Ethics

The study was performed according to the principles of the declaration of Helsinki and ethical guidelines of the Swedish research council. Ethical approval was obtained from the regional vetting board in Umeå (Dnr 2017–141–31 M, 20170530). All participating patients gave informed written consent.

Author contributions

RW and MS designed the project. MA drafted the manuscript. All authors analysed and interpreted the data, as well as revised and approved the final manuscript. RW provided financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.01.031.

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