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ORIGINAL SCIENTIFIC REPORT

Risk Factors for Skin Flap Necrosis in Breast Cancer Patients Treated with Mastectomy Followed by Immediate Breast Reconstruction

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Abstract

Background Skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) are the standard techniques for achieving a cosmetic outcome, but necrosis of a cutaneous flap including the nipple–areolar complex (NAC) is a serious complication. To analyze the risk factors for skin flap necrosis, we retrospectively evaluated a clinical database of breast cancer patients treated with mastectomy followed by immediate breast reconstruction.

Methods Four hundred and twelve cases were consecutively recorded between 2006 and 2016. Body weight (BW), body mass index (BMI), distance from NAC to referent tumor, distance from overlying skin to the tumor and weight of breast resection (WBR) as measured in the operating theater were included in the statistical analysis.

Results NSM, SSM and total mastectomy were performed in 123 (30%), 96 (23%) and 193 cases (47%), respectively. A tissue expander was used in 379 cases (92%), a silicone implant in 8 (2%) and autologous breast reconstruction in 25 (6%). Skin flap necrosis was found in 7% of all cases and NAC necrosis in 13% of NSM cases. In a univariate analysis, BW, NSM and WBR were risk factors for skin flap necrosis, and BW, BMI and WBR were risk factors for NAC necrosis. In a multivariate analysis, NSM and WBR remained significant risk factors for skin flap necrosis, and WBR was a significant risk factor for NAC necrosis.

Conclusions WBR is an important risk factor for skin flap necrosis. Especially, NAC necrosis should be considered for patients with large-volume breasts who undergo NSM and immediate breast reconstruction.

Introduction

In Japan, the number of breast cancer patients continues to increase; approximately, 80,000 new cases are diagnosed annually [1]. With the spread of breast cancer screening, the incidence of early stage breast cancer has also increased. The current treatment strategy for early breast cancer consists of surgery, drug therapy and radiation therapy. In the 1980s, breast-conserving surgery (BCS) dramatically changed breast surgery based on level I evidence from randomized clinical trials that compared BCS to total mastectomy (TM) [2, 3]. Since then, BCS has been the standard care for early breast cancer patients. However, patients are not always satisfied with the cosmetic outcome after BCS. TM and breast reconstruction represents an

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alternative surgical treatment when breast deformity after BCS is strongly expected.

Breast reconstruction is mainly performed by either autoplastic transplantation or a silicone implant. Before 2013, silicone implants were rarely used in Japan, since the cost of such breast reconstruction was not covered by government health insurance. However, since then, there has been a rapid increase in the number of breast reconstructions for early breast cancer patients.

For breast cancer patients whose tumors do not have extensive intraductal spread or direct invasion toward the skin or nipple–areolar complex (NAC), skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) is usually performed instead of TM [4, 5]. When local recurrence and distant metastases for these operations were compared to those for TM, oncologic safety was reported in early breast cancer as well as advanced breast cancer [6–14]. However, skin flap necrosis including the NAC is a major problem after breast reconstruction. Several retrospective studies have shown that diabetes mellitus (DM), body mass index (BMI), smoking history, resection volume of breast and the skin incision site were associated with skin flap necrosis [15–22]. Although other reports had different results regarding these risk factors, the definitive risk factors related to skin flap necrosis are still unclear [18, 20, 22, 23]. To improve the cosmetic outcome for breast cancer patients treated with mastectomy followed by immediate breast reconstructions, we analyzed risk factors for skin flap necrosis from our database.

Materials and methods

This study included consecutive breast cancer cases treated from April 2006 to May 2016. Cases with stage 0 to IIIB or ipsilateral breast tumor recurrence underwent mastectomy followed by immediate breast reconstruction. In most cases, mastectomy was performed by breast surgeons and breast reconstruction was performed by plastic surgeons. Mastectomy consists of TM, SSM and NSM. In brief, TM is performed with resection of whole breast tissue and its overlying skin. SSM is resected with whole breast tissue including NAC and NSM with whole breast tissue with preservation of NAC. Usually, TM was done in cases of large breast tumor with or without skin invasion. When the tumor was small or far from the overlying skin, SSM was favorably undergone. In addition, NSM was planned when the tumor was far from NAC. Anyway, the type of mastectomy depended on physician's choice. The following clinicopathological data were analyzed: age, height, body weight (BW), BMI, smoking history, DM, histological type, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), Ki-67, nuclear grade, T and N classification according to UICC ver.7, primary systemic therapy, pathological stage, type of surgery (NSM, SSM, TM), skin incision site (para-areolar, inframammary, lateral, above tumor), surgeon, weight of breast resection (WBR), type of breast reconstruction (silicone implant, autologous breast reconstruction, tissue expander), distance from NAC to referent main tumor (DNT) and distance from overlying skin to the tumor (DST). Autologous breast reconstruction consisted of transverse rectal abdominal musculocutaneous (TRAM) flap and latissimus dorsi (LD) flap.

ER, PR and Ki-67 were assessed by immunostaining. HER-2 status was assessed by using the HERCEPTEST (Agilent Technologies: Santa Clara, CA) or fluorescence in situ hybridization based on the ASCO/CAP guidelines [24]. DNT and DST were calculated based on the results of MR mammography. In the axial and sagittal sections, the shortest distance in the vertical direction of the nipple from the tumor including the intraductal component was defined as DNT. In the same way, the shortest distance in the vertical direction of the skin from the tumor including the intraductal component was defined as DST [25]. WBR was measured and recorded at the operating theater.

Skin flap necrosis and NAC necrosis were defined as necrotic lesions that should have required additional resection after breast reconstruction. Skin flap necrosis including NAC necrosis was evaluated in all cases, whereas NAC necrosis was only evaluated in NSM cases. The statistical significance of differences was examined using Chi-squared test. The logistic regression model in JMP version 11.0 (SAS Institute, Japan) was used for analysis. Risk factors with a two-sided p value of less than <0.05 were considered to be statistically significant.

Results

Four hundred and twelve cases underwent mastectomy followed by immediate breast reconstruction. Table 1 shows their background characteristics. The median age (range) was 48 years (32 to 78 years). Most cases had early breast cancer with pathological stage 0 to IIB. A few patients had a smoking history (16%) or DM (1.9%). The median BW and BMI (range) were 53 kg (37–91 kg) and 21.5 kg/m^2 (14.8–35.8 kg/m^2), respectively. The surgical procedure and skin flap necrosis are summarized in Table 2. Six breast surgeons mainly performed most of breast surgery. The median WBR (range) was 312 g (50 g to 1048 g). NSM, SSM and TM were performed in 123 (30%), 96 (23%) and 193 cases (47%), respectively. Among them, a para-areolar incision was attempted in only 2.4% of NSM cases. For immediate breast reconstruction, a tissue expander was used in 379 cases (92%), a silicone

Table 1 Patient characteristics

Number of cases (%)	412 (100)
Age at diagnosis [Median, range]	48, 32–78
Height (cm) [Median, range]	154, 141–176
Body weight (kg) [Median, range]	53, 37–91
BMI (kg/m^2) [Median, range]	21.5, 14.8–35.8
Tumor classification	
T0	11 (2.7)
T in site	99 (24.0)
T1	151 (36.7)
T2	123 (29.9)
T3	15 (3.6)
T4	5 (1.2)
Tumor recurrence	8 (1.9)
Node classification	
N0	321 (77.9)
N1	76 (18.5)
N2	12 (2.9)
N3	2 (0.5)
Unknown	1 (0.2)
Pathological stage	
0	95 (23.1)
I	121 (29.4)
IIA	110 (26.7)
IIB	42 (10.2)
IIIA	14 (3.4)
IIIB	7 (1.7)
IIIC	1 (0.2)
pCR	13 (3.2)
Tumor recurrence	8 (1.9)
Unknown	1 (0.2)
Estrogen receptor	
Positive	337 (81.8)
Negative	71 (17.2)
Unknown	4 (1.0)
Progesterone receptor	
Positive	316 (76.7)
Negative	91 (22.1)
Unknown	5 (1.2)
Human epidermal growth factor receptor 2	
Positive	63 (15.3)
Negative	342 (83.0)
Unknown	7 (1.7)
Ki67	
Less than 10%	83 (20.1)
10–30%	111 (26.9)
More than 30%	56 (13.6)
Unknown	162 (39.3)
Nuclear grade	
1	67 (16.3)
2	223 (54.1)
3	89 (21.6)
Unknown	33 (8.0)
Histological type	
DCIS or LCIS	108 (26.2)
IDC	274 (66.5)
ILC	30 (7.3)
Neoadjuvant therapy	
Chemotherapy	79 (19.2)
Endocrine therapy	12 (2.9)
None	320 (77.7)
Unknown	1 (0.2)
Smoking history	
No	263 (63.8)
Yes	66 (16.0)
Unknown	83 (20.1)
Diabetes mellitus	
No	402 (97.6)
Yes	8 (1.9)
Unknown	2 (0.5)

IDC invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *LCIS* lobular carcinoma in site, *NIDC* non-invasive ductal carcinoma, *pCR* pathological complete response

implant in 8 (2%) and autologous breast reconstruction in 25 (6%). Skin flap necrosis and NAC necrosis were recorded in 29 of all 412 cases (7%) and in 16 of 123 NSM cases (13%), respectively.

Figure 1 shows the incidence of skin flap necrosis and NAC necrosis according to the type of breast reconstruction. Skin flap necrosis and NAC necrosis were observed more often in cases with TRAM flap and LD flap than in cases with a silicone implant or tissue expander, but these differences were not significant. However, NSM showed a significantly higher rate of skin flap necrosis than SSM and TM ($p = 0.0033$, Fig. 2). Figure 3 shows the rates of skin flap necrosis and NAC necrosis and their related risk factors. BW and WBR were significantly related to skin flap necrosis and NAC necrosis ($p = 0.0015$ and 0.0006, and $p = 0.0285$ and <0.0001, respectively). Figure 4 shows the relationship between skin flap necrosis and DST or DNT. There were no significant differences in the incidences of skin flap necrosis and DST or DNT. Similar results were found for NAC necrosis and DST or DNT.

In a univariate analysis, higher BW, NSM and higher WBR were risk factors for skin flap necrosis ($p = 0.0115$, 0.0033 and 0.0006, respectively), and higher BW, higher BMI and higher WBR were risk factors for NAC necrosis ($p = 0.0285$, 0.0478 and <0.0001, respectively) (Table 3). Smoking history is known as a risk factor for skin flap

Table 2 Surgical parameters

Number of cases (%)	412 (100)
Type of surgery	
NSM	123 (29.9)
SSM	96 (23.3)
TM	193 (46.8)
Method of IBR	
Silicone	8 (1.9)
Autologous BR	25 (6.1)
Tissue expander	379 (92.0)
Surgeon	
A	77 (18.7)
B	28 (6.8)
C	43 (10.4)
D	75 (18.2)
E	130 (31.6)
F	7 (1.7)
G	40 (9.7)
Others	12 (2.9)
WBR (g) [Median, range]	312, 50–1048
≦200	75 (18.2)
200< ≦ 400	165 (40.0)
400< ≦ 600	70 (17.0)
600<	48 (11.7)
Unknown	54 (13.1)
Incision site in 123 cases of NSM	
Para-areolar	1 (0.8)
Inframammary	14 (11.4)
Lateral	97 (78.9)
Above tumor	5 (4.1)
Para-areolar and inframammary	1 (0.8)
Para-areolar and lateral	1 (0.8)
Unknown	4 (3.2)
Resection of necrotic tissues	
Skin in all cases	29 (7.0)
Silicone	1 (12.5)
Tissue expander	24 (13.3)
TRAM flap	2 (20)
LD flap	2 (13.3)
NAC in 123 NSM cases	16 (13.0)
Silicone	0 (0)
Tissue expander	14 (12.5)
TRAM flap	1 (13.1)
LD flap	1 (12.5)

BR breast reconstruction, *IBR* immediate breast reconstruction, *LD* latissimus dorsi; *NAC* nipple–areolar complex, *NSM* nipple-sparing mastectomy, *SSM* skin-sparing mastectomy, *TM* total mastectomy, *TRAM* transverse rectal abdominal musculocutaneous, *WBR* weight of breast resection

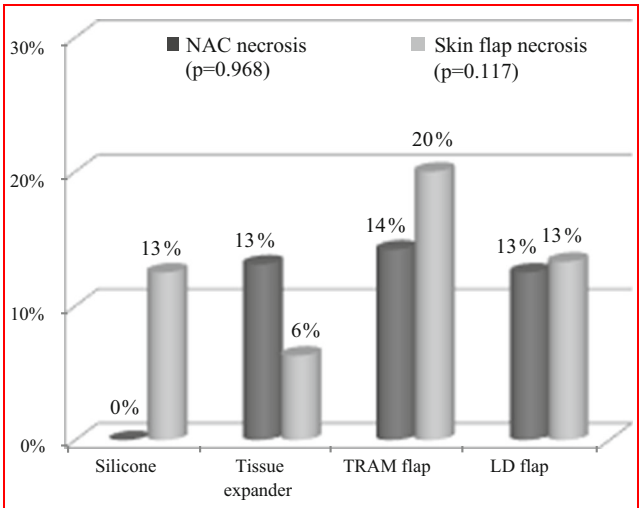

Fig. 1 Rate of necrosis according to type of immediate breast reconstruction. *LD* latissimus dorsi, *NAC* nipple–areolar complex, *TRAM* transverse rectal abdominal musculocutaneous. *p* value in the parenthesis was determined using Chi-squared test

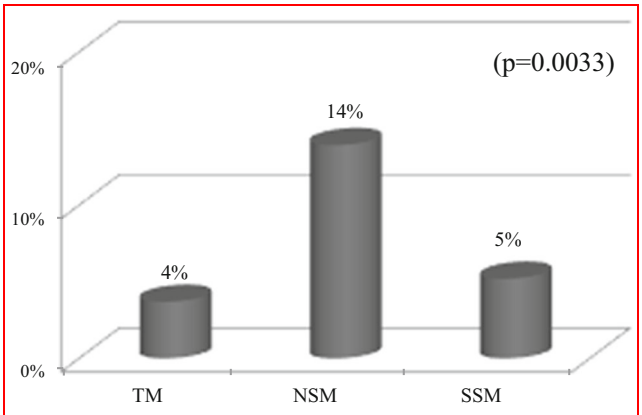

Fig. 2 Rate of necrosis due to type of surgery. *NSM* nipple-sparing mastectomy. *SSM* skin-sparing mastectomy, *TM* total mastectomy. *p* value in the parenthesis was determined using Chi-squared test

necrosis. Primary systemic therapy including neoadjuvant chemotherapy may also damage skin condition and induce ischemic change of skin flap. However, smoking history and primary systemic therapy had no statistical significance regarding risk factors for skin flap necrosis. The incidence rates were observed in 10% and 5% of cases with smoking history or not, and in 6% and 6% of cases treated with primary systemic therapy or not, respectively.

From this analysis, several factors with p value <0.2 and DNT and DST were included in a multivariate analysis, but BMI was excluded because BMI was correlated with BW

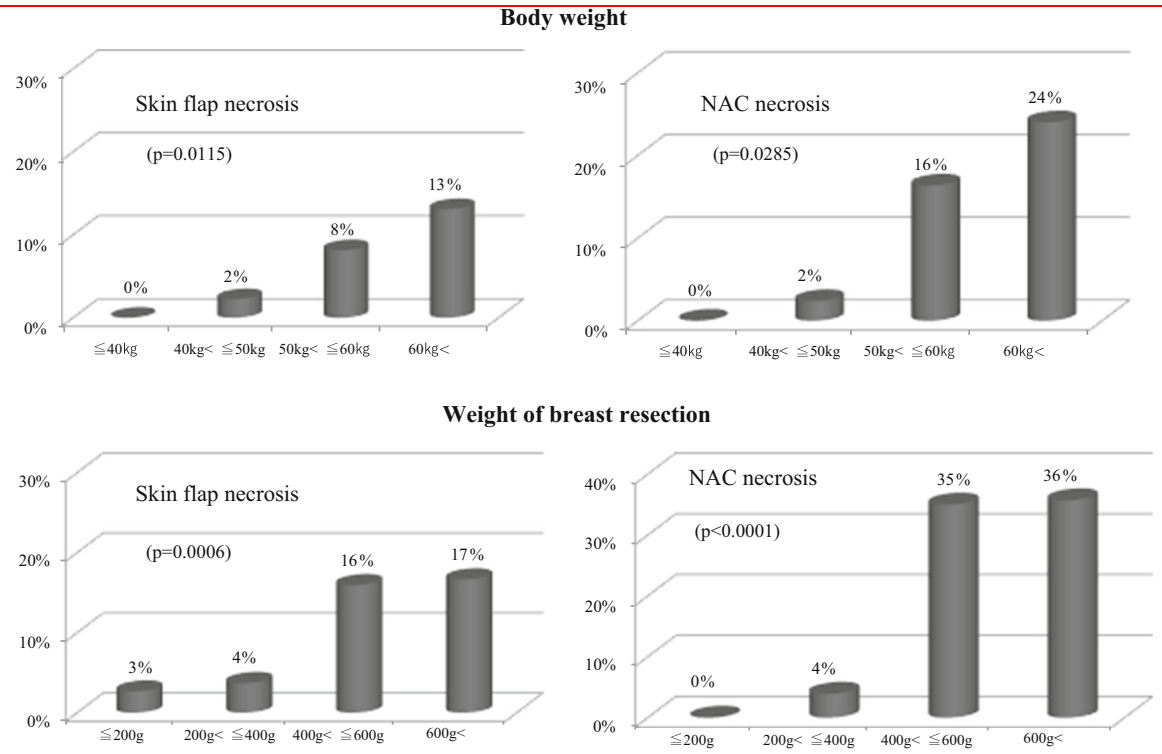

Fig. 3 Relationships between clinical factors and necrosis. *NAC* nipple–areolar complex. *p* value in the parenthesis was determined using Chi-squared test

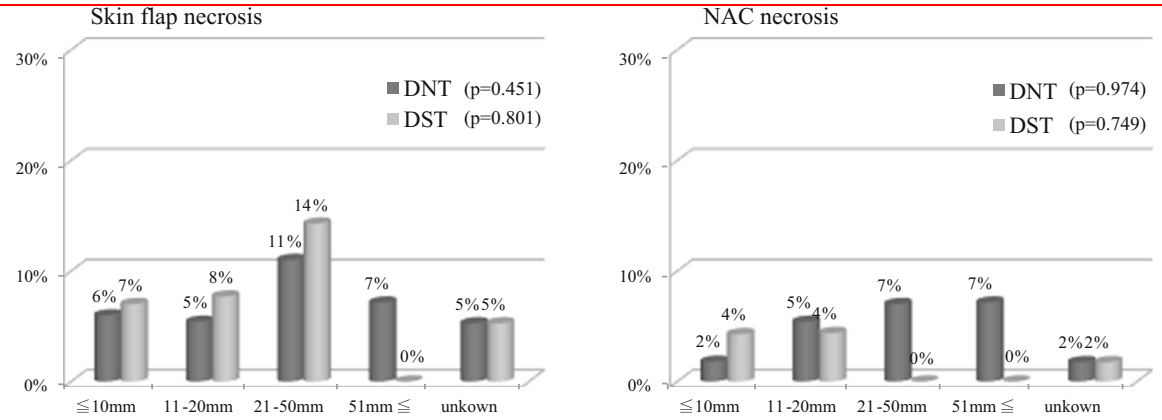

Fig. 4 Rate of necrosis according to distance from tumor to skin and NAC. *DNT* distance from NAC to referent tumor, *DST* distance from overlying skin to the tumor, *NAC* nipple–areolar complex. *p* value in the parenthesis was determined using Chi-squared test

as a confounding factor. From the results, NSM and higher WBR remained statistically significant for skin flap necrosis ($p = 0.0052$ and 0.0008, respectively) and higher WBR was significant for NAC necrosis ($p = 0.0136$) (Table 4).

Discussion

We investigated risk factors for skin flap necrosis after mastectomy followed by immediate breast reconstruction. WBR was an important factor for skin flap necrosis, as previously reported [15, 17, 19]. One possible explanation for this result is that blood flow in the skin flap may decrease in cases that require an extensive surgical

Table 3 Univariate analysis (p value)

Risk factor	Skin flap necrosis	NAC necrosis
Age	0.264	0.126
Height	0.862	0.964
Body weight	0.0115	0.0285
Body mass index	0.148	0.0478
Smoking history	0.250	0.806
Diabetes mellitus	0.589	0.357
Histological type	0.255	0.920
Estrogen receptor	0.653	0.484
Progesterone receptor	0.798	0.387
HER2	0.797	0.967
Ki67	0.607	0.507
Nuclear grade	0.224	0.623
DNT	0.451	0.974
DST	0.801	0.749
Pathological stage	0.413	0.789
Tumor classification	0.549	0.879
Node classification	0.376	0.876
Primary systemic therapy	0.495	0.502
Incision site in NSM cases	0.918	0.898
Type of surgery	0.0033	–
Surgeon	0.478	0.340
WBR	0.0006	<0.0001
Method of IBR	0.117	0.968

DNT distance between nipple–areolar complex and tumor, *DST* distance between skin and tumor, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *IBR* immediate breast reconstruction, *WBR* weight of breast resection

Table 4 Multivariate analysis (p value)

Risk factor	Skin flap necrosis	NAC necrosis
Age	–	0.5271
Body weight	0.3561	0.5833
DNT	0.5776	0.8996
DST	0.4740	0.6407
Type of surgery	0.0052	–
WBR	0.0008	0.0136
Method of IBR	0.0764	–

DNT distance between nipple–areolar complex and tumor, *DST* distance between skin and tumor, *IBR* immediate breast reconstruction, *WBR* weight of breast resection

maneuver under the skin. Another possible explanation is that the subdermal vascular plexus may be damaged in patients with a large breast, because the skin flap may be easily crushed by surgical retraction during the operation. In our study, the incidence of skin flap necrosis including NAC necrosis was very high in patients with WBR of 400 g or more (Fig. 3). In several reports, patients with a BMI $\geqq 25$ kg/m^2 had a high risk of skin flap necrosis [15, 17, 19]. In this study, although BW was a risk factor for skin flap necrosis in a univariate analysis, it was not an independent risk factor in a multivariate analysis.

To our knowledge, this is the first study to analyze the relationship between skin flap necrosis and DNT or DST, albeit no statistical significance was found. Our hypothesis is that shorter DNT or shorter DST may be related to higher incidence of skin flap necrosis or NAC necrosis. However, Fig. 4 reveals no statistical relationship among them. One explanation is that patients with longer DST might have larger breasts, which might be associated with higher BW. When patients were divided into 3 groups according to DST, the proportion of patients with BW of 60 kg or more was 57% in patients with DST of 21 mm or more, but only 35% in those with DST of 11–20 mm and 15% in those with DST of 0 to 10 mm. Thus, DST had no significant power hidden behind BW.

There have been some reports about the relationship between the skin incision site and NAC necrosis [15, 16, 20, 22]. A lateral skin incision has been reported to be a good cosmetic approach for avoiding NAC necrosis [16, 20, 22], while a para-areolar skin incision was a risk factor for NAC necrosis [20, 22]. In this study, the skin incision site was not associated with NAC necrosis, because a lateral skin incision was made in 80% of NAC cases and a para-areolar skin incision was used in only 2.4%.

This study has some limitations. First, the results were drawn from a retrospective database. The incidence rate of NAC necrosis seemed to be very high (13%) as reported previously [15, 16, 20, 22]. One reason is that skin flap necrosis in our hospital was very strictly recorded. Thus, debridement of tiny or small necrotic lesion that had been done without local anesthesia is included in database. Unfortunately, the degree of debridement and/or additional skin closure could not be searched. Second, the decision-making about breast surgery and breast reconstruction depended on patient's choice and physician's discretion. There was no clear consensus about mastectomy followed by immediate breast reconstruction among breast surgeons and plastic surgeons. Third, other risk factors for skin flap necrosis such as thickness of skin flap, hematoma and wound dehiscence were not recorded in most cases. Fourth, indocyanine green angiography demonstrated risk reduction of skin flap necrosis by immediate breast reconstruction [26]. This technique should be applied for prevention of skin flap necrosis.

In conclusion, WBR was found to be an important risk factor for skin flap necrosis. The risk of NAC necrosis is higher in women with large-volume breasts, and other

options than NSM have to be discussed in preoperative information.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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