The Associated Clinicopathologic Characteristics of Nipple-Areola Complex Involvement in Breast Cancer

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Abstract

Background. At present, the indication for nipple-sparing mastectomy (NSM) remains inconclusive, and the occult NAC involvement is one of the most considerable problem when carrying out NSM. We aimed at identifying the predictive factors of NAC involvement, to provide an implement of selecting suitable NSM candidates.

Methods. The association between the NI and tumorous clinicopathologic characteristics of 272 mastectomies and 31 therapeutic NSM performed in our hospital from 2016 to 2018 were retrospectively evaluated.

Results. 38 of 272 (14.0%) mastectomies and 2 of 31 (6.5%) NSM were confirmed to have NAC involvement, and all the intraoperative frozen section examination of the sub-areolar/nipple tissue were consistent with the permanent section examination in NSM. The median follow-up durations for NSM was 24 months, local recurrence occurred in 1 of 30 (3.2%) patients. Among 272 mastectomies, the NAC involvement showed significant association with the abnormal nipple signs ($P=0.001$), tumor size ≥ 4 cm measured by ultrasound ($P=0.001$) and gross pathologic samples ($P=0.001$), tumor-nipple distance ≥ 1 cm ($P=0.003$), central location ($P=0.001$), lymph node metastasis ($P=0.004$) and HER2 overexpression ($P=0.023$). A preoperative predictive model of NAC involvement utilizing nipple signs (normal or abnormal), tumor size (≤ 4 cm or ≥ 4 cm), tumor location (central or peripheral) showed a PPV of 85.7% and a NPV of 90.3%.

Conclusions. The local recurrence rate after NSM is low (3.2%) in our study, and the intraoperative frozen section examination plays an important role in the procedure of NSM. Further more, we proposed a predictive model of the NAC involvement utilizing the preoperative tumorous characteristics, including the nipple signs, tumor size measured by ultrasound, and the tumor location. This predictive model could be working in the planning of breast cancer surgery.

Background

Breast cancer is one of the three most common carcinomas in the world, which endangered both physical and psychological health of numerous women. With locoregional and systemic therapy advancing, more importance are attached to the patients' survival and quality of life [1, 2]. Nipple-sparing mastectomy (NSM) removes the whole breast tissue, previous biopsy incisions, and the skin overlying superficial tumors, preserving the nipple-areola complex (NAC), which promotes the cosmetic outcomes of breast cancer surgery effectively. As an indispensable part of the breast, nipple-areola complex preservation would bring much higher psychological satisfaction and improve the quality of life [3, 4]. Published studies have showed a low incidence of local cancer recurrence after NSM in selected patients [4-10]. Whether the NAC being involved or not, is decisive condition for carrying out NSM effectively and safely. In order to improve the accuracy of suitable patients' selection, it is necessary to evaluate the predictive factors of NAC involvement. As reported, the rates of NAC involvement in breast cancer ranged

from 5.6% to 58%, this disparity may result from differentiation of subjects the researchers had chosen, histologic sampling methods and definition of positive NAC margin. The correlated clinicopathologic characteristics were also proposed in several studies, such as tumor size, tumor location, tumor-Nipple distance (TND) [11-14].

This retrospective study had analyzed the rates of NAC involvement in mastectomy and NSM as well as its correlation with each clinicopathologic characteristics. We expected to observe the outcome of NSM, identify the associated factors in mastectomy and proposed a predictive model that can be useful in the surgical planning.

Methods

Three hundred female patients diagnosed as breast carcinoma between 2016 and 2018 in our hospital were included in our study, 270 patients received mastectomies, 30 patients received therapeutic NSM and breast reconstruction. We conducted NSM for patients who had wish to have NAC preservation and breast reconstruction, exclude only women with imaging evidence of NAC involvement, locally advanced breast cancer, inflammatory breast cancer, Paget's disease.

All the information were extracted from case management system of our hospital, such as age, clinical nipple signs (nipple signs would be deemed as abnormality if there present nipple discharge, bleeding, retraction, ulceration, palpable mass, skin thickened). Tumor size was recorded in both preoperative ultrasound and gross pathologic samples. Tumor location was categorized to central/retroareolar and peripheral tumors. The shortest distance between tumor and nipple was measured as tumor-nipple distance (TND) on pathologic samples. The tumor multicentricity/multifocality was defined as more than one lesion of invasive carcinoma separated by benign tissue.

The identification of tumor cells in the nipple margin sections would be defined as positive, and we deemed NAC to be involved if they contained invasive cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), or Paget's disease. For mastectomy samples, the pathologic examination was done by vertical section of the nipple at 2 mm intervals, the sections were then stained using H&E stain and immunohistochemical staining method. For NSM, a separately submitted retro-areolar tissue was sent to intraoperative frozen section examination as a nipple margin and followed by paraffin sectioning examination.

The patients who underwent NSM were followed up, getting regular physical examination and further imaging tests if necessary, including computed tomography of the chest or brain, bone scan, and liver ultrasonography. Patients who were absent from examination would be contacted by telephone to confirm whether they were alive.

Student's T-test was used to evaluate continuous variables, and the chi-square test or Fisher's exact test was used to evaluate categorical variables. Binary Logistic regression was then performed to form a predictive model of NAC involvement. Only $P \leq 0.05$ was considered statistically significant. The

relationship between the tumor ultrasound size and histopathologic size was analyzed by Pearson Correlation Coefficient .Statistical calculations were performed by SPSS software (version 26.0).

Results

A total of 272 standard mastectomies and 31 nipple-sparing mastectomies were conducted, 40 cases(13.2%) has NAC involvement. As showed in table 1,we compared the characteristics of patiens in mastectomy group and NSM group.Despite there was no significant difference in NAC involvement between two groups,the NSM group had a lower incidence of NAC involvement than mastectomy group.For all mastectomies and NSM,the frequency of NAC involvement was 14.0%,6.5% respectively $P=0.373$.Moreover, the significant difference had been observed in age and tumor size. patients in NSM group were yonger and had smaller tumor size than those in mastectomy group (mean age was 47 ± 60 respectively $P\leq0.05$.mean ultrasound size was 1.90cm,2.42cm respectively, $P\leq0.05$.mean histopathologic size was 2.18cm,2.88cm respectively, $P\leq0.05$).The difference of lymph node status,tumor location,and nipple signs were not statistically significant.However,compared to mastectomy group, patients underwent NSM tended to have negative lymph node,peripheral tumor and normal nipple signs.

Among 30 patients who were planing to receive NSM, 1 patient underwent bilateral NSM.2 patients are proved to have a positive nipple margin.One of them converted to mastectomy due to identifying tumor cells in intraoperative frozen section of the submitted nipple margin.Another patient whose pathological examination showed lobular carcinoma in situ involving lactiferous ducts choosed to preserve the NAC.Nonetheless,it turned out no evidence of involment in the removing NAC at the routine paraffin sections after surgery.All the results of intraoperative frozen section were consistent to final paraffin sections.

In a median follow-up duration of 24 months (range 3-42 months),none of 29 patients occurred distant metastasis.Only one patient was diagnosed as metastasis of rib 13 months after the operation and received local excision. All patients were confirmed to be alive at the last follow-up.

Table 1. Tumorous Clinicopathologic Features of Patients In Mastectomy And NSM

	Mastectomy	NSM	P
Total	272	31	
NAC involvement	38[14.0%]	2[6.5%]	0.373
Age[mean]	60y	47y	0.042
Mean tumor size[US]	2.42cm	1.90cm	0.023
Mean tumor size[P]	2.88cm	2.18cm	0.023
Positive lymph node	114[41.9%]	10[32.2%]	0.300
Central location	40[14.9%]	1[3.2%]	0.129
Abnormal nipple signs	18[6.6%]	1[3.2%]	0.824

For the 272 mastectomies, the NAC involvement has no statistical correlation with patients age, tumorous multicentric/multifocal, tumor type, histologic grade, estrogen receptor or progesterone receptor status, and Ki67 status[Table 2]. We observed that nipple signs, tumor size measured by ultrasound and gross pathologic samples, tumor-nipple distance, tumor location, lymph node metastasis and HER2 overexpression all influenced the occurrence of nipple involvement. The presence of abnormal nipple signs increase vulnerability to NAC involvement, and the rates of NAC involvement are 55.6%[11.0%] respectively ($P=0.001$). Patients with tumor ultrasound size $\leq 4\text{cm}$ had incidence of 36.7%[10.3%] ($P=0.001$). Patients with tumor histopathologic size $\leq 4\text{cm}$ had incidence of 41.2%, 9.7% ($P=0.001$). Of NAC positive tumors 50% were $\leq 1\text{cm}$ from nipple, while 88.7% NAC negative tumors were $\geq 1\text{cm}$ from nipple ($P=0.003$). The associations between tumor ultrasound size, tumor histopathologic size, and TND were also statistically significant when calculated as continuous variables ($P=0.001$, $P=0.001$, and $P=0.04$, respectively). Cases with tumor in central location had a higher incidence of NAC involvement than those tumor in peripheral location (45.0%, 7.9% respectively) ($P=0.001$). Of NAC positive cases 63.2% occurred lymph node metastasis, while 38.5% NAC negative tumors were lymph node positive ($P=0.004$). Patients with HER2 overexpression were also more likely to have NAC involvement ($P=0.023$).

Meanwhile, we analyzed the correlation between tumor ultrasound size and tumor histopathologic size by Pearson Correlation Coefficient ($r=0.610$, $P=0.001$). It was indicated that ultrasound provide a useful function in reflecting the actual tumor histopathologic size.

Among these clinicopathological factors associated with NAC involvement, we selected three predictive factors which can be obtained by physical examination and ultrasound test preoperatively. The nipple

signs(normal or abnormal),tumor size(≤ 4 cm or >4 cm),tumor location(central or peripheral) were used to develop a predictive model by Binary Logistic regression $\chi^2=45.49$ P

Table 2.NAC Involvement And Tumorous Clinicopathologic Characteristics

Characteristics	NAC Involvement			P Value
	Total	Negative	Positive	
Age	272			0.600
≤50	118	103[87.3%]	15[12.7%]	
>50	154	131[85.1%]	23[14.9%]	
Nipple signs	272			0.001
Normal	254	226[89%]	28[11.0%]	
Abnormal	18	8[44.4%]	10[55.6%]	
Tumor size[US]	253			0.001
≤4cm	223	200[89.7%]	23[10.3%]	
>4cm	30	19[63.3%]	11[36.7%]	
Tumor size[P]	251			0.001
≤4cm	217	196[90.3%]	21[9.7%]	
>4cm	34	20[58.8%]	6[41.2%]	
TND[P]	67			0.003
≤1cm	13	6[46.2%]	7[53.8%]	
>1cm	54	47[87%]	7[13%]	
Tumor Location	268			0.001
Peripheral	228	210[92.1%]	18[7.9%]	
Central	40	22[55.0%]	18[45.0%]	
Multicentric/focal	268			0.135
Yes	44	35[79.5%]	9[20.5%]	
No	224	197[87.9%]	27[12.1%]	
Tumor Type	229			0.843
IDC	167	142[85.0%]	25[15.0%]	
ILC	12	10[83.3%]	3[16.7%]	
DCIS	20	18[90.0%]	2[10.0%]	
Histology Grade[IDC]				0.553

I	16	1381.2%	318.2%
II	144	12486.1%	2013.9%
III	83	7489.2%	910.8%
Lymph Node Metastasis			
	272		0.004
Negative	158	14491.1%	148.9%
Positive	114	9078.9%	2421.1%
HER2			
	270		0.023
Negative	41	4097.6%	12.4%
Positive	229	19384.3%	3615.7%
ER			
	270		0.294
Negative	78	7089.7%	810.3%
Positive	192	16384.9%	2915.1%
PR			
	270		0.447
Negative	80	7188.8%	911.2%
Positive	190	16285.3%	2814.7%
Ki-67			
	270		0.737
≤10%	67	5785.1%	1014.9%
>10%	203	17686.7%	2713.3%

Table 3. Logistic regression of the predictive factors for NAC involvement

Factors		OR95%CI	P value
Tumor location	Peripheral	1.0	0.001
	Central	11.64.5-29.9	
Nipple signs	Normal	1.0	0.003
	Abnormal	8.82.1-36.6	
Tumor sizeUS	≤4cm	1.0	0.01
	>4cm	4.71.4-15.2	

Table 4. Probability of NAC involvement by logistic regression model

Location		Nipple signs		Tumor size (US)		Probability (%)
Central	Peripheral	Abnormal	Normal	≥4cm	<4cm	
+		+		+		95.4
+		+			+	81.7
+			+	+		*
+			+		+	33.6
	+	+		+		*
	+	+			+	27.7
	+		+	+		16.9
	+		+		+	4.1

*lack of data

0.001). which PPV was 85.7%, and the NPV was 90.3%—the specificity was 99.6%, the sensitivity was 20.0%.Patients with tumors in central location were nearly 11.6 times more likely to have a positive nipple than patients with tumors in peripheral location(OR 11.6—95% CI 4.5 to 29.9). The odds ratio for predicting NAC involvement by abnormal nipple signs increased to 8.8 (95% CI 2.1–36.6) when considering patients with normal nipple. Patients with tumors >4cm were nearly 4.7 times more likely to have NAC involvement than patients with tumors ≤4cm(OR 4.7—95% CI 1.4 to 15.2).The probabilities of NAC involvement in different condition were showed in table 4.

Discussion

Mastectomy is inevitable for some breast cancer patients,due to tumor size,tumor multicentric,type of tumor,or other reasons.The NSM and breast reconstruction technique provide a viable choice for these patients.NSM retains the natural envelope of the skin and nipple areola complex,achieving excellent aesthetic results. Nevertheless,the preservation of NAC has also raised concern about occult nipple involvement,which has been discussed in many studies.In our study,the incidence of NAC involvement of patients underwent mastectomy and NSM were 14.0%—6.5% respectively.The former was similar to the incidence reported in several studies [15-19]. The difference between this two groups may resulted from that—our surgeons has the inclination to select patients with normal nipple,smaller tumor size,peripheral tumor,and negative lymph node.However,of merely 30 cases in our study,the NAC involvement incidence in NSM may be underestimated.

The local cancer recurrence rates(1.7-10.3%) after NSM have been reported in published studies[8, 20-22], but they had different patients inclusion criteria and duration of follow-up. Smith et al performed NSM for stages 0 to 3 breast cancer patients who had no clinical or imaging evidence of NAC involvement,the rate of local recurrence was 3.7%(median follow-up duration of 51 months).In a study by Kim et al,the incidence of local recurrence was only 2% during a median follow-up of 60 months.The indication of preserving NAC was any stage, any tumor size, and any tumor areola distance tumors with clinically normal nipple. Burdge et al found a local recurrence of 10.3% in patients with locally advanced disease (71.8 % lymph node status was positive,average tumor size was 3.8cm.),and the median follow-up duration was 18 months.During a median follow-up of 24 months in our research,we found the local recurrence was low(3.2%) after NSM,and all patients survived at the last follow-up.To some extent,we had validated the oncological safety of NSM in selected patients.

According to the recommendation of latest NCCN guidelines(2020.v3), the nipple-areolar complex (NAC) could be preserved in cancer patients selected by experienced multidisciplinary teams.Paget's disease, nipple discharge associated with cancer,and imaging evidence of the nipple or subareolar tissues involvement should be excluded,and nipple margin assessment is definitely needed.However,the standard assessment of NSM candidates and indications are still undefined and inconsistent.In our study,frozen section examination of nipple margin(retro-areolar tissue) were conducted in all NSM cases,whose results were all consistent to permanent paraffin sections.One patient sacrificed the NAC due to a positive nipple margin in NSM,but the removed NAC turned out no cancer involved.Smith et al used frozen sections rarely in the procedure of NSM,because they deemed that frozen section was less accurate than permanent pathologic examination,and has difficulty in distinguishing benign atypia from ductal carcinoma in situ (DCIS)[21].In a study by D'Alonzo, a discoid specimen beneath the base of the nipple was obtained as nipple margin.They found that the sub-areolar/nipple tissue assessment had a sensitivity of 42.3% in predicting nipple involvement.Though the frozen sections showed a great concordance(92.1%) with final paraffin-embedded sections,it should be careful to remove the NAC when DCIS was diagnosed in the frozen section examination[23]. Additionally, Ponzone suggested to perform double intra-operative assessment of subareolar ducts and proximal nipple ducts,to increase the sensitivity of intraoperative pathological assessment[24].

Meanwhile,we observed that patients with abnormal nipple signs(nipple discharge,bleeding,retraction, ulceration,palpable mass, skin thickened) were more likely to have NAC involvement($P=0.001$). Billar found abnormal nipple signs or symptoms had a 61% sensitivity,86% specificity, 45% positive predictive value (PPV), and 92% negative predictive value (NPV) for determining NAC involvement [17].Though as one of the most common symptoms in breast cancer, nipple discharge is not the contraindication of NAC preservation if there was no evidence of tumor invasion to nipple margin.Since nipple discharge is not necessarily the outcome of tumor invasion to NAC, and NAC only acts as a drain channel when breast cancer invades ducts far from the NAC[25].As reported,TND,tumor size,tumor location,lymph node status,and HER2 overexpression showed significantly correlation with NAC involvement[26-28],which also had been demonstrated in our study.Weidong et al reported that patients with $TND \leq 3\text{cm}$,pathological tumor size $\geq 2.5\text{cm}$,central tumor, lymph node metastasis or HER2 overexpression were at higher risk of

getting NAC involved [27]. Additionally, they considered the lymphatic vascular invasion (LVI) as another crucial predictive factor, which had been mentioned in other studies as well [29]. Gulben et al categorized patients into different risk groups by using tumor location, number of axillary lymph node status, and LVI. Patients with two or three risk factors were classified among the high-risk group, and patients with no or one risk factor were classified among the low risk group. The possibility of NAC involvement was 11.4 times higher in high-risk group compared to low risk group [30].

Though the effects of tumor size and TND had been confirmed, it has not been clearly determined the exactly cut-off figures on imaging or pathology. Study showed that the possibility of NAC involvement was lower when TND ≥ 1 cm measured by mammography or MRI. Especially for MRI, its NPV and PPV of predicting NAC involvement were 100%, 39% respectively [26]. Steen et al found TND ≥ 2 cm, tumor size ≥ 2 cm measured by MRI were significantly associated with nipple involvement [31]. A study of patients with carcinoma in situ by Hwang et al reported that short TND and suspicion of nipple involvement on mammographic or MRI were predictive factors of NAC involvement, but ultrasound findings were not significantly correlated with NAC involvement. However, Lim found the tumors contacting or invading the nipple on US was significantly correlated with nipple involvement [32]. In our research, all patients accepted ultrasound test preoperatively, which described and recorded the tumor location and tumor size. We found the incidence of NAC involvement in patients with tumor ultrasound size ≥ 4 cm ≤ 4 cm were 36.7% $\sim$ 10.3% respectively ($P < 0.001$). Tumor size measured by ultrasound was significant predictive factors of NAC involvement, and Pearson correlation coefficient analysis demonstrated preoperative ultrasound can accurately represent histopathologic tumor size. Therefore, we confirmed the functional role of preoperative ultrasound test and recommend to apply it in the management of NSM.

As for the predictive model, A recent study produced a preoperative predictive model using seven factors, including MRI tumor size ≥ 4 cm, mammographic TND ≥ 1 cm, MRI TND ≥ 1 cm, MRI nipple enhancement, central tumor, multicentric/multifocal, clinical node involvement. Each factor scores 0 or 1 point, and the total scores were categorized into low (0–3), intermediate (4), or high (5–7) risk group. Patients in high risk group were recommended to sacrifice the NAC, and patients in the intermediate risk group who hoped to preserve NAC could undertake the frozen section examination [33]. Besides, another study by Wang et al proposed a model consisting of tumor location, nuclear grade, and HER2 expression [28]. Schecter et al reported a formula for predicting NAC involvement based on tumor size, TND and stage, which was found to have a sensitivity of 92%, specificity of 77% [34]. The models developed in these studies are basing on more costly image testing or preoperative biopsy. The factors including pathological TND, tumor size, number of metastatic lymph node, HER2 overexpression were generally known after surgery. Whereas, parameters of the predictive model in our study are much more easier to obtain. Basing on ultrasound tumor size, tumor location, and nipple signs, a predictive model were proposed to provide the possibility of NAC involvement. We found breast cancer patients with abnormal nipple signs, in central location, and tumor size ≥ 4 cm, were most likely to develop NAC involvement (95.4%); patients with normal nipple signs, tumor in peripheral location, and tumor size ≤ 4 cm had a lowest possibility (4.1%) of NAC involvement.

Conclusion

In summary,our study shows that the local recurrence rate after NSM is low 3.2%in our research.NSM appears to be an oncologically safe procedure for selected patients with negative nipple margin.NAC involvement had a incidence of 14.0% in mastectomy patientsand was associated with the nipple signs,tumor location,tumor size measured by ultrasound or gross pathologic samples,tumor-nipple distance,lymph node metastasis,HER2 overexpression.We developed a predictive model based on nipple signs,tumor size and tumor location,which aimed to improve the accuracy of selecting eligible patients for NSM,by combining with pathological examination of retro-areolar tissue,to conduct NSM safely.

Declarations

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Authors'contributions

HWL, HZN, JH ,MT and CL collected and interpreted the patient data, and HWL was a major contributor in writing the manuscript. Lixi inspired the topic selection and led the authors. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The protocol of prospective study was approved by the Ethics Committee of The 3rd Affiliated Hospital of Sun Yat-sen University.

Consent for publication

Not applicable.

Competing interests

All authors declare no potential conflicts of interest.

References

1. Harbeck N, Gnant M. Breast Cancer. *Lancet*. 2017; 10074: 1134-50.
2. Veronesi U, Stafyla V, Petit JY, Veronesi P. Conservative Mastectomy: Extending the Idea of Breast Conservation. *Lancet Oncol*. 2012; 7: e311-7.
3. Mota BS, Riera R, Ricci MD et al. Nipple- and Areola-Sparing Mastectomy for the Treatment of Breast Cancer. *The Cochrane database of systematic reviews*. 2016; 11: D8932.
4. Gerber B, Krause A, Reimer T et al. Skin-Sparing Mastectomy with Conservation of the Nipple-Areola Complex and Autologous Reconstruction is an Oncologically Safe Procedure. *Ann Surg*. 2003; 1: 120-7.
5. Wu ZY, Kim HJ, Lee JW et al. Breast Cancer Recurrence in the Nipple-Areola Complex After Nipple-Sparing Mastectomy with Immediate Breast Reconstruction for Invasive Breast Cancer. *Jama Surg*. 2019; 11: 1030-7.
6. Jensen JA, Jensen JA, Orringer JS, Orringer JS, Giuliano AE, Giuliano AE. Nipple-Sparing Mastectomy in 99 Patients with a Mean Follow-up of 5 Years. *Ann Surg Oncol*. 2011; 6: 1665-70.
7. De La Cruz L, Moody AM, Tappy EE, Blankenship SA, Hecht EM. Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple–Areolar Recurrence in the Setting of Nipple-Sparing Mastectomy: A Meta-Analysis and Systematic Review. *Ann Surg Oncol*. 2015; 10: 3241-9.
8. Burdge EC, Yuen J, Hardee M et al. Nipple Skin-Sparing Mastectomy is Feasible for Advanced Disease. *Ann Surg Oncol*. 2013; 10: 3294-302.
9. Wagner JL, Fearmonti R, Hunt KK et al. Prospective Evaluation of the Nipple-Areola Complex Sparing Mastectomy for Risk Reduction and for Early-Stage Breast Cancer. *Ann Surg Oncol*. 2012; 4: 1137-44.
10. Orzalesi L, Casella D, Santi C et al. Nipple Sparing Mastectomy: Surgical and Oncological Outcomes From a National Multicentric Registry with 913 Patients (1006 Cases) Over a Six Year Period. *The Breast*. 2016; 75-81.
11. Menon RS, van Geel AN. Cancer of the Breast with Nipple Involvement. *Br J Cancer*. 1989; 1: 81-4.
12. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The Incidence of Occult Nipple-Areola Complex Involvement in Breast Cancer Patients Receiving a Skin-Sparing Mastectomy. *Ann Surg Oncol*. 1999; 6: 609-13.
13. Tang R, Coopey SB, Merrill AL et al. Positive Nipple Margins in Nipple-Sparing Mastectomies: Rates, Management, and Oncologic Safety. *J Am Coll Surgeons*. 2016; 6: 1149-55.
14. Mallon P, Feron J, Couturaud B et al. The Role of Nipple-Sparing Mastectomy in Breast Cancer: A Comprehensive Review of the Literature. *Plast Reconstr Surg*. 2013; 5: 969-84.
15. Kissin MW, Kark AE. Nipple Preservation During Mastectomy. *The British journal of surgery*. 1987; 1: 58-61.
16. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of Nipple/Areolar Involvement with Mastectomy: Can the Areola be Preserved? *Ann Surg Oncol*. 2002; 2: 165-8.
17. Billar JAY, Dueck AC, Gray RJ, Wasif N, Pockaj BA. Preoperative Predictors of Nipple-Areola Complex Involvement for Patients Undergoing Mastectomy for Breast Cancer. *Ann Surg Oncol*. 2011; 11: 3123-

8.

18. Vyas JJ, Chinoy RF, Vaidya JS. Prediction of Nipple and Areola Involvement in Breast Cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 1998; 1: 15-6.
19. Eisenberg RE, Chan JS, Swistel AJ, Hoda SA. Pathological Evaluation of Nipple-Sparing Mastectomies with Emphasis On Occult Nipple Involvement: The Weill-Cornell Experience with 325 Cases. *Breast J*. 2014; 1: 15-21.
20. Krajewski AC, Boughey JC, Degnim AC et al. Expanded Indications and Improved Outcomes for Nipple-Sparing Mastectomy Over Time. *Ann Surg Oncol*. 2015; 10: 3317-23.
21. Smith BL, Tang R, Rai U et al. Oncologic Safety of Nipple-Sparing Mastectomy in Women with Breast Cancer. *J Am Coll Surg*. 2017; 3: 361-5.
22. Kim HJ, Park EH, Lim WS et al. Nipple Areola Skin-Sparing Mastectomy with Immediate Transverse Rectus Abdominis Musculocutaneous Flap Reconstruction is an Oncologically Safe Procedure: A Single Center Study. *Ann Surg*. 2010; 3: 493-8.
23. D'Alonzo M, Pecchio S, Campisi P et al. Nipple-Sparing Mastectomy: Reliability of Sub-Areolar Sampling and Frozen Section in Predicting Occult Nipple Involvement in Breast Cancer Patients. *Eur J Surg Oncol*. 2018; 11: 1736-42.
24. Ponzzone R, Maggiorotto F, Carabalona S et al. MRI and Intraoperative Pathology to Predict Nipple-Areola Complex (NAC) Involvement in Patients Undergoing NAC-sparing Mastectomy. *Eur J Cancer*. 2015; 14: 1882-9.
25. Chang RY, Cheung PS. Nipple Preservation in Breast Cancer Associated with Nipple Discharge. *World J Surg*. 2017; 1: 176-83.
26. D Alonzo M, Martincich L, Biglia N et al. Clinical and Radiological Predictors of Nipple-Areola Complex Involvement in Breast Cancer Patients. *Eur J Cancer*. 2012; 15: 2311-8.
27. Weidong L, Shuling W, Xiaojing G et al. Nipple Involvement in Breast Cancer: Retrospective Analysis of 2323 Consecutive Mastectomy Specimens. *Int J Surg Pathol*. 2011; 3: 328-34.
28. Wang J, Xiao X, Wang J et al. Predictors of Nipple-Areolar Complex Involvement by Breast Carcinoma: Histopathologic Analysis of 787 Consecutive Therapeutic Mastectomy Specimens. *Ann Surg Oncol*. 2012; 4: 1174-80.
29. Vlajcic Z, Zic R, Stanec S, Lambasa S, Petroveckii M, Stanec Z. Nipple-Areola Complex Preservation: Predictive Factors of Neoplastic Nipple-Areola Complex Invasion. *Ann Plas Surg*. 2005; 3: 240-4.
30. Gulben K, Yildirim E, Berberoglu U. Prediction of Occult Nipple-Areola Complex Involvement in Breast Cancer Patients. *Neoplasma*. 2009; 1: 72-5.
31. Steen ST, Chung AP, Han S, Vinstein AL, Yoon JL, Giuliano AE. Predicting Nipple-Areolar Involvement Using Preoperative Breast MRI and Primary Tumor Characteristics. *Ann Surg Oncol*. 2013; 2: 633-9.
32. Lim S, Park G, Choi HJ, Kwon WJ, Kang BS, Bang M. Use of Preoperative Mammography, Ultrasonography, and MRI to Predict Nipple Areolar Complex Involvement in Breast Cancer. *Br J*

Radiol. 2019; 1102: 20190074.

33. Seki H, Sakurai T, Mizuno S et al. A Novel Nipple-Areola Complex Involvement Predictive Index for Indicating Nipple-Sparing Mastectomy in Breast Cancer Patients. *Breast Cancer-Tokyo*. 2019; 6: 808-16.
34. Schecter AK, Freeman MB, Giri D, Sabo E, Weinzweig J. Applicability of the Nipple-Areola Complex-Sparing Mastectomy: A Prediction Model Using Mammography to Estimate Risk of Nipple-Areola Complex Involvement in Breast Cancer Patients. *Ann Plas Surg*. 2006; 5: 498-504.