



A Study of Involvement of Nipple Areola Complex in Carcinoma Breast to Devise an Algorithm for its Preservation

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Authors' contributions

This work was carried out in collaboration between both authors. All patients were admitted under author AKM workup was done by author AL under the guidance of author AKM patients were operated on by author AKM specimens were sectioned and marked by author AL. The conception of the study was by author AL data was collected, recorded, and compiled by author AL the final proofreading was done by author AKM. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: This study is conducted to assess the involvement of nipple-areola complex in patients of carcinoma breast who are undergoing mastectomy, to develop criteria to preserve the nipple-areola complex. This would prevent its unnecessary removal while promoting its preservation.

Materials and Methods: This prospective study has been carried out in the Department of General Surgery, in SOUTH EASTERN RAILWAY HOSPITAL, KOLKATA, India, between November 2018 to October 2020. The histopathological reports were studied to derive factors predisposing to nipple-areola complex involvement.

Results: Analysis reveals that patients with tumors in multiple quadrants, subareolar location, multifocal or multicentric tumors, large size, advanced grade, Her-2-neu positive with significant lymph nodes, and tumors in the vicinity of the nipple-areola complex are poor candidates for nipple-areola sparing mastectomy. The analysis also reveals that age, BMI, parity, side of breast involved or ER and PR status do not have any bearing on Nipple areola sparing mastectomy.

Conclusion: Nipple areola sparing mastectomy is a viable option in carcinoma breast patients undergoing curative surgery.

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1. INTRODUCTION

From its inception in 1894 until the 1960s, Halsted's radical mastectomy was considered as the standard of care for patients with carcinoma breast undergoing curative surgery. It was conceived in 1894 and was popular till the late 1960s. Subsequently, when Patey reported the modified radical mastectomy (MRM); there was a drop in the local recurrence rate to 10 percent after 10 years of surgery [1]. Further down, Toth and Lappert [2] in 1991 chronicled the skin-sparing mastectomy (SSM). It includes removal of the entire breast along with the nipple-areola complex (NAC) but the skin enveloping the breast and the native inframammary crease (IMC) were left intact. As can be seen that surgeons are keen on preserving more and more of the breast as much as is possible and removing only what is necessary. It stands to reason that a surgeon preserves the nipple and the areola principally due to aesthetic reasons. This does indeed lead to patients being more satisfied with the procedure and psychologically comforted [3].

Conventional mastectomy involves surgical excision of the breast parenchyma with an ellipse of skin including the nipple-areola complex. The apprehension was that the NAC may have microscopic tumour deposits. There have been trials in large population samples reporting the NAC to be involved in up to 58% percent of cases whereas clinically they appeared to be noninvolved [4]. This concern made the NAC sparing surgery not so popular, with the populace being largely skeptical of the on cological safety, which to some extent, exist even in present times [5,6].

Breast cancer surgeries are becoming more and more tissue preserving as time goes by. Decisions regarding surgery and associated treatment modalities are now being extensively discussed in multidisciplinary tumor boards. A woman who is diagnosed with carcinoma breast has the persistent fear for the longevity of her life and also, the mutilation and perhaps complete loss of her body part(s). Concomitantly, breast-conserving surgery (BCS) leaves patients with the constant question of whether any tumor cells have been left behind after surgery. Thus there has been considerable interest in finding out a feasible alternative. Skin sparing and nipple-

areola complex sparing mastectomy (NASM) provides such a solution where the removal of the breast parenchyma is done while preserving the overlying skin envelope as much as possible.

This study is conducted to assess the involvement of nipple-areola complex in patients with carcinoma breast who are undergoing mastectomy, to develop criteria to preserve the nipple-areola complex. This would prevent its unnecessary removal while promoting its preservation.

2. MATERIALS AND METHODS

This is a prospective study which has been carried out in the Department of General Surgery, in south eastern railway central hospital, which is a tertiary level hospital of Kolkata between November 2018 to October 2020.

2.1 Study Population

Patients of carcinoma breast subjected to mastectomy with excision of the nipple-areola complex.

2.2 Statistical Software

SPSS version 20 has been used for the analysis.

2.3 Sample Size

The study is a cross sectional study in which prospective observations have been made.

$$N (\text{sample size}) = z_{\alpha}^2 p(1-p) / e^2$$

Where p is proportion and e is precision

Here $\alpha = 5\%$ hence $z_{\alpha} = 1.96$

p: Incidence rate of carcinoma breast in India is 25.8 per every 1, 00, 000 [7]

e = 0.5%.

Using the aforementioned values in the formula, n comes out as 40.

Hence a minimum of 40 patients needed to be included in the study.

We have a sample size of 60.

2.4 Statistical Analysis

Carcinoma breast tumors have been analyzed as to whether they have nipple-areola involvement or not. Apart from the descriptive analysis that is presented by percent of tumors with or without nipple involvement in each subgroup, the *P* values from Fisher's exact test and Chi-square test are provided as an index to indicate the difference between subgroups on the proportion of cancers with nipple involvement. The logistic regression is then used to develop an algorithm to predict nipple involvement under different patient characteristics.

2.5 Inclusion Criteria

- 1) Female patients with cytologically proven breast carcinoma.

2.6 Exclusion Criteria

- 1) Patients denying consent.
- 2) Male breast Carcinoma.
- 3) Inoperable breast carcinoma.
- 4) Grossly and radiologically involved NAC.
- 5) Inflammatory breast cancer.
- 6) Skin involvement

2.7 Methodology

Following approval from the Ethics Committee of Central Hospital, South Eastern Railway, written informed consent has been taken from all the patients before they participated in this study. The patients have been adequately assessed by the surgeon, an anesthetist and if required, the cardiologist. The patients have been admitted the day before surgery and the procedure has been clearly explained. They were monitored from the day before surgery till the time of discharge. The day of operation was defined as day 0, the day after as day 1 and so on.

2.8 Parameters Studied

Age, BMI, Parity, clinical staging, tumor location, (e.g., upper inner, upper outer, lower inner, lower outer, central or in multiple quadrants), tumor type (invasive ductal carcinoma [IDC], invasive lobular carcinoma [ILC] or both), multifocality (defined as two or more tumor foci present < 4 cm apart from each other), multicentricity (defined as two or more tumor foci present > 4 cm apart from each other), tumor size (<1 cm, 1–2 cm, 2–5 cm, and, >5 cm), histological grade (according to the

modified Bloom-Richardson grading system), nuclear grade (using the 3-tier grading system), expression of estrogen receptor (ER), progesterone receptor (PR), and HER2, lymph node status (recorded as present or absent both clinically or radiologically), lymphovascular invasion and MRI tumor to nipple distance were reviewed and recorded.

2.9 Study Techniques

1. All the patients with carcinoma breast admitted in our ward were subjected to a detailed history using a structured questionnaire (see pro forma) and examined clinically.
2. Baseline investigations of the patients were done which included hemoglobin (Hb), total leucocyte count (TLC), differential leucocyte count (DLC), erythrocyte sedimentation rate (ESR), platelet count, sodium (Na+)/potassium(K+), fasting and postprandial blood sugar levels, renal function test, liver function test, PT/INR, electrocardiogram (ECG), chest X-ray, CECT Abdomen (if required), CECT Thorax (if required), Bone Scan (if required) and PET-CT Scan (if required).

2.10 Operative Procedure

Excision of nipple-areola complex along with mastectomy and axillary lymph node clearance (MRM)

2.11 Postoperatively

All mastectomy specimens were inked and sections were made with each section measuring 1-cm-thick. The nipples were shaved and sectioned into 2–3-mm thick tissue sections and submitted for microscopic examination. The areolas were shaved and submitted as such. The presence of tumor deposits in any of these sections was taken to be as NAC involvement.

3. RESULTS AND ANALYSIS

The present study is a randomized prospective clinical study done on patients attending South Eastern Railway Central Hospital and selected for modified radical mastectomy. The sample size is 60. Categorical variables are expressed as the number of patients and percentage of patients and compared across the groups using Pearson's Chi-Square Test for Independence of Attributes/ Fisher's Exact Test as appropriate.

Continuous variables are expressed as Mean and Standard Deviation and compared across the groups using an unpaired t-test. An alpha level of 5% has been taken, i.e. p-value less than 0.05 is significant.

On assessment of the study population, it was found that out of the 60 patients studied, 33 had NAC involvement and 27 had no NAC involvement.

The first parameter to be studied was age, where the population was divided among a range of 10 years starting from 21 years. People with no NAC involvement were 3, 4, 12, 6, and 2 in the 21-30, 31 – 40, 41-50, 51-60 and 61-70 age group respectively. While on the other hand, there were 0,12,9,7 and 5 in the same age groups respectively.

The population was divided into BMI less than 25 kg/m² and more than 25 kg/m². 17 women had NAC involvement and 17 had no involvement with BMI <25 whereas 16 women had NAC involvement and 7 had none with BMI >25. This gave a p-value of 0.054, thus making BMI an insignificant determinant.

Parity was also deemed insignificant with a p-value of 0.456. A total of 33 women had NAC involvement and 27 didn't.

Involvement of the left or right breast did not seem to affect nipple-areola complex

involvement with a p-value of 0.311, thus making it insignificant.

Lymph nodal presence seems to be a major factor. 24 women out of 31 with lymphovascular invasion had NAC involvement (p-value <0.001). Also, 21 women out of 27 with palpable lymph nodes had NAC involvement while only 9 out of 29 women with no lymph nodes had NAC involvement (p: 0.001). This suggests lymph node involvement restricts the use of nipple-areola sparing mastectomy. Also, Nodal staging has a significant bearing (p: 0.001).

The next parameter studied was the number of quadrants of the breast the tumor was occupying. Analysis showed that with tumors occupying multiple quadrants, all had NAC involvement (p: 0.000). Furthermore, analysis of involved quadrants and NAC involvement reveals significant association as p-value is 0.003 with more propensity of NAC involvement with subareolar tumor.

The hormone receptor status always has played a major role in cases of breast cancer. Analysis reveals that estrogen receptor (p: 0.157) and progesterone receptor status (p: 0.077) has no bearing on nipple-areola involvement. Out of the 33 women with NAC involvement, 16 were positive for estrogen receptors while 17 were negative. Similarly, 12 were positive for progesterone receptor and 21 were negative.

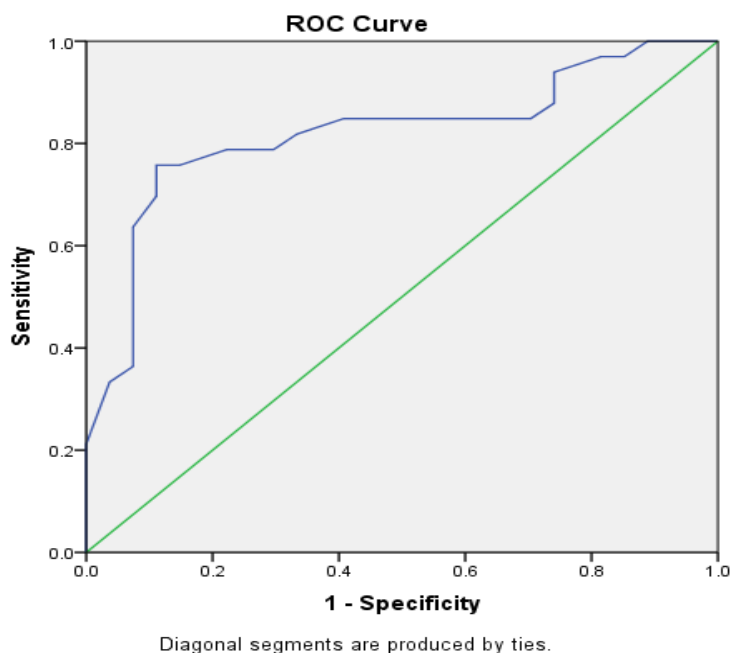


Fig. 1. Tumor size

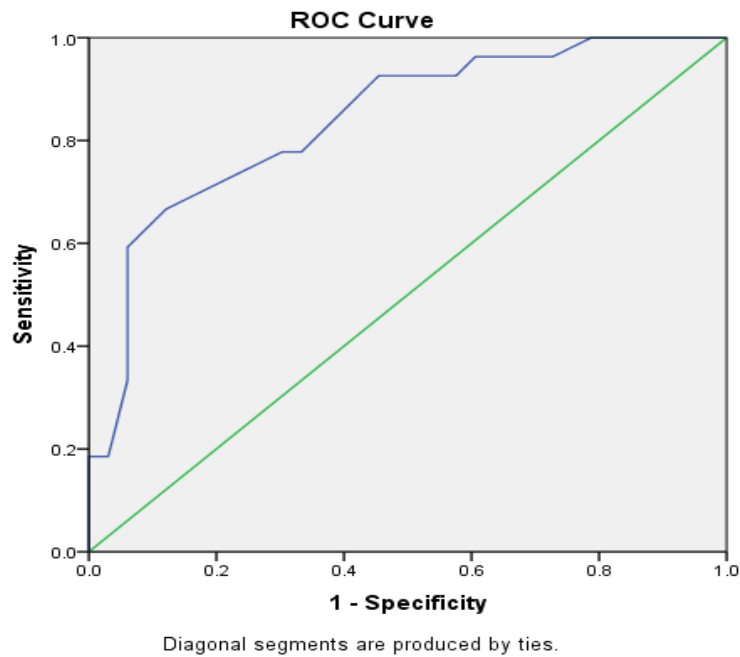


Fig. 2. ROC analysis reveals NAC involvement to be significant at MRI Tumor to nipple Distance less than 2.25 cm with p values less than 0.05

Tables 1 and 2. Analysis of tumor size with NAC involvement reveals significant association as p-value is less than 0.05 with more propensity of NAC involvement with tumor size more than 4.05 cm as described by ROC analysis

Table 1.

Area Under the Curve			
Test result variable(s): Tumor size			
Area	p-Value	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
0.820	<0.001	0.710	0.931

Cut Offs from ROC is 4.05

Table 2.

		Tumor Size		Total	p-Value	Significance
		<4.05	>=4.05			
NAC Involvement	NO	24	3	27	<0.001	Significant
	YES	8	25	33		

Tables 3, 4 and 5. This suggests that tumors at a distance of less than 2.25 cm on MRI from the nipple-areola complex have a higher chance of NAC involvement and thus nipple-areola sparing mastectomy should be avoided in these patients

Table 3.

Area	p-Value	Asymptomatic 95% Confidence Interval	
		Lower Bound	Upper Bound
0.839	<0.001	0.738	0.940

Table 4.

Cut Offs from ROC is 2.25

		MRI Tumor to Nipple Distance (cm)		Total	p-Value	Significance
		>2.25	<=2.25			
NAC	No	18	9	27	<0.001	Significant
Involvement	Yes	4	29	33		

Table 5.

Scoring system	TP	TN	FP	FN	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
MRI TND (cm) <=2.25	29	18	9	4	87.88	66.67	76.32	81.82	78.33

4. DISCUSSION

NSM is a viable treatment option for patients with carcinoma breast, but much stress has to be laid upon patient selection. Meticulous patient selection could decrease the NAC excision, thus promoting cosmesis and at the same time, not compromising on oncological safety. Local recurrence rates could thus be comparable to that of conventional mastectomy. Many women prefer to preserve the nipple after mastectomy for a better cosmetic outcome. For this reason, this study has been done to investigate the differences between breast cancer patients with and without NAC involvement and demonstrated the predictors of NAC involvement to enable the selection of patients who may be candidates for NAC preservation while maintaining oncological safety. It is hereby attempted to identify some of the pre-operative factors that could help in making a better decision regarding nipple-areola sparing mastectomy.

The study is a cross-sectional study in which prospective observations have been made, with a sample size of 60.

NAC involvement in our patient pool was 55% with 33 out of 60 patients having involved NAC. This is comparable to other study populations, where nipple involvement (NI) ranges from 0 to 58% [8].

In this study, analysis of age (p: 0.085), BMI (p: 0.044), parity (p: 0.456) and breast side (p: 0.311) with NAC involvement reveals no significant association. Similar results were obtained by Faisal et al. [9] and Wang et al. [10] in their respective studies.

Analysis of LVI and NAC involvement reveals a significant association as the p-value is less than 0.05 with more propensity of NAC involvement with LVI presence. Three studies [11,12,13] had statistical analysis confirming that LVI is associated with higher rates of NI. Similarly, analysis of the presence of significant lymph nodes and NAC involvement reveals a significant association with high chances of NAC involvement. This is confirmed by the study of 787 mastectomy specimens by Wang et al. [10].

Comparison of T stage and NAC involvement reveals significant association with more propensity of NAC involvement with higher T stage, that is, more the tumor size, more is the chance of NAC involvement. ROC analysis of this study also tells us that a tumor size of more than 4.05 cm has a very high probability of NAC involvement. This has been confirmed by numerous studies such as Wang et al. [10] which states the tumor size to beyond 5 cm for the NAC to be involved. Another study by Abdelhamid et al. [14] and Faisal et al. [9] states the tumor mass to be 4cm at maximal diameter to be the statistically significant safe size for having an NAC free of malignancy.

Analysis of N stage and NAC involvement reveals significant association as p-value is less than 0.05 with more propensity of NAC involvement with higher N stage as confirmed by Faisal et al. [9].

Analysis of the number of involved quadrants and NAC involvement reveals significant association as p-value is less than 0.05 with more propensity of NAC involvement with tumor extending to multiple quadrants and more

Chart 1. Analysis reveals the p-value to be 0.085 which makes age an insignificant parameter for NAC involvement

		Age					Total	p-Value	Significance
		21-30	31-40	41-50	51-60	61-70			
NAC Involvement	No	3(100)	4(25)	12(57.14)	6(46.15)	2(28.57)	27(45)	0.085	Not Significant
	Yes	0(0)	12(75)	9(42.86)	7(53.85)	5(71.43)	33(55)		
Total		3(100)	16(100)	21(100)	13(100)	7(100)	60(100)		

Chart 2. There was a slight propensity for NAC involvement in pre-obese women, although, as stated earlier, insignificant

		BMI (kg/m ²)		Total	p-Value	Significance
		<25	>=25			
NAC Involvement	No	20(54.05)	7(30.43)	27(45)	0.044	Significant
	Yes	17(45.95)	16(69.57)	33(55)		
Total		37(100)	23(100)	60(100)		

Chart 3. The maximum NAC involvement was seen in women with 2 children, with the incidence decreasing at either extreme, that is, with no children or >4 children. But as stated earlier, this was insignificant

		Parity						Total	p-Value	Significance
		P0	P1	P2	P3	P4	P5			
NAC Involvement	NO	1(100)	6(60)	11(40.74)	7(43.75)	1(20)	1(100)	27(45)	0.456	Not Significant
	YES	0(0)	4(40)	16(59.26)	9(56.25)	4(80)	0(0)	33(55)		
Total		1(100)	10(100)	27(100)	16(100)	5(100)	1(100)	60(100)		

Charts 4-5. Higher the nodal staging, more the chances of NAC involvement, with all women with N2 stage having NAC involvement

		LVI		Total	p-Value	Significance
		No	Yes			
NAC Involvement	NO	20(68.97)	7(22.58)	27(45)	<0.001	Significant
	YES	9(31.03)	24(77.42)	33(55)		
Total		29(100)	31(100)	60(100)		

		LN		Total	p-Value	Significance
		NO	YES			
NAC Involvement	NO	21(63.64)	6(22.22)	27(45)	0.001	Significant
	YES	12(36.36)	21(77.78)	33(55)		
Total		33(100)	27(100)	60(100)		

Charts 6-7. Minimal involvement was seen in the upper outer and lower inner quadrants

		Quadrant		Total	p-Value	Significance
		Single	Multiple			
NAC Involvement	NO	27(56.25)	0(0)	27(45)	0.000	Significant
	YES	21(43.75)	12(100)	33(55)		
Total		48(100)	12(100)	60(100)		

		Location					Total	p-Value	Significance
		A	B	C	D	E			
NAC Involvement	NO	8(88.89)	3(42.86)	9(90)	4(44.44)	3(23.08)	27(56.25)	0.003	Significant
	YES	1(11.11)	4(57.14)	1(10)	5(55.56)	10(76.92)	21(43.75)		
Total		9(100)	7(100)	10(100)	9(100)	13(100)	48(100)		

Chart 8. Multifocal and multicentric tumors exclude nipple-areola sparing mastectomy due to the high involvement of NAC (p <0.001)

		Multifocality / Multicentricity		Total	p-Value	Significance
		NO	YES			
NAC Involvement	NO	27(57.45)	0(0)	27(45)	<0.001	Significant
	YES	20(42.55)	13(100)	33(55)		
Total		47(100)	13(100)	60(100)		

Charts 9-10. For determining significant MRI Tumor to nipple distance and tumor size, non-parametric receiver operating characteristic (ROC) curve analysis was done, and ROC curves were used to evaluate the accuracy of MRI TND (cm) and Tumour Size to predict NAC Involvement, indicated by the area under the curve (AUC). The "optimum cut-off point" was determined, as the cut-off point with the highest [(sensitivity + specificity)/2] ratio, at which there was a maximal correct prediction NAC Involvement

		Histological Grade			Total	p-Value	Significance
		Grade 1	Grade 2	Grade 3			
NAC Involvement	NO	19(95)	7(21.88)	1(12.5)	27(45)	<0.001	Significant
	YES	1(5)	25(78.13)	7(87.5)	33(55)		
Total		20(100)	32(100)	8(100)	60(100)		

		Nuclear Grade			Total	p-Value	Significance
		GRADE 1	GRADE 2	GRADE 3			
NAC Involvement	NO	12(92.31)	14(38.89)	1(9.09)	27(45)	<0.001	Significant
	YES	1(7.69)	22(61.11)	10(90.91)	33(55)		
Total		13(100)	36(100)	11(100)	60(100)		

Charts 11-12. This shows that estrogen and progesterone receptors are unevenly distributed among women with involved nipple-areola complex

		ER		Total	p-Value	Significance
		NO	YES			
NAC Involvement	NO	9(34.62)	18(52.94)	27(45)	0.157	Not Significant
	YES	17(65.38)	16(47.06)	33(55)		
Total		26(100)	34(100)	60(100)		

		PR		Total	p-Value	Significance
		NO	YES			
NAC Involvement	NO	11(34.38)	16(57.14)	27(45)	0.077	Not Significant
	YES	21(65.63)	12(42.86)	33(55)		
Total		32(100)	28(100)	60(100)		

Chart 13. Her-2-neu receptor status is significant in the fact that positive patients were having more incidence of nipple-areola complex involvement (p: <0.001). Out of the 33 women with NAC involvement, 26 were positive for HER-2-neu

		HER		Total	p-Value	Significance
		NO	YES			
NAC Involvement	NO	22(75.86)	5(16.13)	27(45)	<0.001	Significant
	YES	7(24.14)	26(83.87)	33(55)		
Total		29(100)	31(100)	60(100)		

chances of NAC involvement with subareolar tumor. Faisal et al.[9], Wang et al.[10] and Mallon et al. [4] all have similar results. A systematic review of literature by Headon et al. [15] confirms the same.

Comparison of histological grade and NAC involvement and nuclear grade and NAC involvement reveals significant association as p-value is less than 0.05 with more propensity of NAC involvement with higher histological grade and nuclear grade. This has been supported and similar results were obtained by Wang et al. [10] and Faisal et al. [9].

Analysis of ER status, PR status, and HER 2 Neu status with NAC involvement reveals no association of NAC involvement with ER and PR status, but a higher propensity of NAC involvement in HER 2 Neu positive cases. This has been supported by numerous studies such as Headon et al. [15], Wang et al. [10] and Mallon et al. [4].

ROC analysis reveals NAC involvement to be significant at MRI TND less than 2.25 cm. Faisal et al.in their study derived a value of 2.4 cm, Vyas et al.[16] found a TND of 2.5 cm to be significant and Mallon et al. [4] describe the minimum TND for free NAC to be 2 cm.

5. CONCLUSION

Analysis of the data revealed that certain criteria can help us make an informed decision regarding which patients to select for a nipple-areola sparing mastectomy while providing oncological safety.

Analysis reveals that patients with tumors which

- extend to multiple quadrants
- are subareolar in location
- are multifocal or multicentric
- larger than 4.05 cm
- histological or nuclear grade III
- HER 2 neu positive
- significant lymphadenopathy
- LVI positive
- Less than 2.25 cm away from the nipple are poor candidates for nipple-areola sparing mastectomy. The analysis also reveals that age, BMI, parity, side of breast involved or ER and PR status do not have any bearing on the selection of patients for NASM.

6. LIMITATIONS

- Prospective observations have been made based on the data of this study. So more the number of patients, more is the accuracy even though a significant number of patients (n= 60) were included in this study.We must keep in mind that this study is exploratory in nature, intending to promote similar studies to popularise NSM.
- Data was collected from a tertiary health care center which is a referral hospital for the entire South-Eastern Railway employee population and their families as well. So, the results cannot be extrapolated to the total population.
- To study the long-term effects and outcomes of NAC preservation, longer follow-up and more studies are required.
- This study does not take into account the patients who have or will receive chemotherapy or radiotherapy.

CONSENT AND ETHICAL APPROVAL

The study was approved by the Ethical Committee of South Eastern Railways, Central Hospital. Patient confidentiality was maintained throughout the study and informed and written consent was taken from all patients included in the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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