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Research Article

NEOADJUVANT CHEMOTHERAPY INDUCED HISTOPATHOLOGICAL CHANGES IN BREASTCANCER: A STUDY OF 35 CASES IN NORTH INDIA

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A B S T R A C T

Purpose: The objective of the present study was to evaluate pathological response based on morphologic details to neoadjuvant chemotherapy (NACT) in treatment of breast cancer which can help to predict prognosis.
Methods: It was a descriptive study of 35 cases, where microscopic slides of trucut biopsies and modified radical mastectomy (MRM) specimens before and after NACT were examined by pathologist for morphological details.
Results: The mean tumour size before and after NACT was 4.65 and 3.04 cm respectively ($p<0.001$). The median cellularity in pre and post NACT specimens were 60% and 50% respectively ($p<0.001$). Post NACT, out of35, 5.71% were stage IA, 17.14% were stage IIA, 25.73% were stage IIB, 20% were stage IIIA, 2.85% were stageIIIB and 8.57% were stage IIIC. Total 7 cases were stage 0 as they had complete pathologic response. Post NACT, many histomorphological changes (nuclear, cytoplasmic, stromal) in affected as well as adjacent normal breast were statistically significant ($p<0.05$). Pathologic response was complete in 20%, partial in 54.28% and no response in24.72% cases.
Conclusions: NACT causes morphological alterations in cancerous as well as surrounding healthy tissue. Pathologic evaluation of the tumour response is gold standard. Post NACT staging of tumour is better predictor of survival. This ensures that the role of the pathologist is extremely important in correct diagnosis as well as grading of the tumour. It helps in an effective and planned regimen of the therapy leading to better prognosis.

INTRODUCTION

Cancer incidence and mortality are growing at a vigorous pace across the globe and this transition is most striking among emerging economies. Globally, one fourth i.e., 2.1million cases of all female cancer diagnosed in 2018 were of breast cancer.[1]

In India, the age-adjusted incidence rate of breast cancer was 25.8 per 1,00,000 women, making it the leading cancer among Indian females in 2012. According to National Cancer Registry Programme and GLOBOCAN 2018, there were 1,62,468 new cases and 87,090 deaths due to breast cancer in India.[2] In a developing country like India, the delay in seeking medical help and hence detection of malignancy at advanced stages leads to high death rates.[3] Histopathological examination is the better predictor for an accurate diagnosis of breast cancers than fine needle aspiration cytology (FNAC) and mammography. Immunohistochemistry (IHC) markers aid not only in classification but also the targeted therapy. Treatment and prognosis depend on the various clinical and histopathological factors including tumour size, type of tumour, hormonal receptor status, type of therapy provided and most significantly; tostage the cancer.[4]

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The treatment for locally advanced breast cancer typically includes neo-adjuvant chemotherapy (NACT), surgery and radiation therapy with or without endocrine therapy depending on hormone receptor status. NACT was first introduced in early 1980 and was aimed for inoperable, locally advanced breast carcinoma in order to down-size the tumour to attain operable size. Later, it was used in women with operable and earlier stage breast carcinoma so as to become eligible for breast conservation surgery and achieve better outcome.[5,6] It also offered the advantage to minimize micro metastasis.[7]

Assessment of response to chemotherapy can be done by two ways; assessment of clinical and pathologic response. Later is preferred as it provides the possibility of assessment of the treatment efficacy in vivo allowing modification of chemotherapeutic agent in patients with insignificant response and insight in the benefit of the same NACT regime if continued postoperatively. [7,8]

Pathological response is an important prognostic indicator, particularly the complete pathologic response which is associated with improved long-term outcome. Moreover, the presence and extent of residual tumour determines rate of local recurrence and plays a decisive role for the need of further loco-regional and systemic therapy.[9]

There are many existing pathologic response evaluation systems and new ones are continuously emerging but awell-established standardized one to create uniformity in reporting and guide further evaluation/treatment is still deficient. Further, the inexperience of pathologist can create new challenges.[9,10]

Hence, this study was planned to evaluate the pathological response based on morphologic details like cytological, nuclear and stromal changes to NACT in the treatment of breast cancer which can help to predict further treatment and survival of patients.

MATERIALS AND METHODS

Study design

It was a comparative descriptive study conducted at a tertiary health care hospital in north India over a period of 24months from January 2019 to December 2020. Informed consent with all the available demographic, clinical, radiological, serological, histological, IHC, FNAC details and treatment history were taken. Trucut biopsies were taken before NACT and MRM specimens were received after NACT treatment in the department of Pathology, where they were processed with standard protocols and examined by pathologist for morphological details of tumourcells.

Inclusion criteria

All patients diagnosed with stage II and III (T1-T4, N0-2 and M0) breast cancer who received NACT were included.

Exclusion criteria

1. Patients who underwent surgery without chemotherapy.
2. Patients in whom pre NACT biopsy was either unavailable or unsatisfactory for evaluation.
3. Patients where NACT was started following a diagnosis of malignancy made on FNAC.
4. Patients who didn't receive chemotherapy in our institution (avoiding non uniformity of treatment).
5. Patients with distant metastasis (stage IV).

Response Evaluation

National Surgical Adjuvant Breast and Bowel Protocol B-18 (NSABP) was used to evaluate the pathologic response after NACT.[11]

The responses were categorized as

1. Pathologic Complete Response (pCR): No recognizable invasive tumour cells present.
2. Pathologic Partial Response (pPR): Presence of scattered individual or small clusters of tumour cells in adesmoplastic or hyaline stroma.
3. Pathologic No Response (pNR): Tumours not exhibiting the changes listed above.

Sample size

Sample size was calculated at 95% confidence level, alpha error 0.05. At 13% absolute allowable error in analyzing histopathological changes, required sample size was 35 cases.

Ethics

The approval of the Institute Ethics committee was taken before commencing the study. The consent of each patient was obtained prior to the starting of the study. Patient confidentiality was maintained during all research procedures.

Statistical analysis

The statistical analysis was performed by using quantitative as well as qualitative statistics. Quantitative data was expressed in the form of Mean±SD. Qualitative data was analysed by proportions and tables while various morphological features were analysed for their frequency and compared with the final diagnosis using appropriate test of significance (Paired "t" test and Chi square test). The software used in the analysis was SPSS22.0 (IBM Corp. Released 2015. IBM Statistics for Windows, Version 20.0: Armonk, New York, United States) and graph pad PRISM 5.0 version and $p<0.05$ is considered as level of significance.

RESULTS

The patients ranged from 35-75 years, the mean age being 53.86 ±10.13. The majority of patients were in 5th decade (n=12, 34.28%). All of the patients were females. Chief complaint was only lump in the affected breast (45.71%),lump with mastalgia (34.28%), nipple discharge (11.42%) and ulcer (8.57%). Tumour was located in right breast in24 (68.57%) and left breast in 11 cases (31.43%). It was located in upper outer quadrant in 22 (62.85%), upper innerquadrant in 5 (14.28%), lower outer quadrant in 3 (8.57%), retroareolar in 3 (8.57%) and in lower inner quadrant in2 (5.71%) cases. There were 34 cases of infiltrating duct carcinoma not otherwise specified (IDS NOS) and one case of lobular carcinoma both before and after NACT.

In present study, the tumour size before NACT was calculated clinically or radiologically. Pathological tumour size(pT) was calculated according to ypTNM, AJCC 'y' post neoadjuvant chemotherapy classification system in each case. The mean of tumour size before and after NACT was 4.65 and 3.04 cm respectively and the reduction was statistically significant ($p<0.001$) [Table 1].

Table 1 Tumor size before and after NACT

Tumor size in cm	Number of cases before NACT (%)	Number of cases after NACT (%)	p-value
<2cm	0 (0)	6 (21.43)	
2-5cm	24 (68.57)	16 (57.14)	
>5cm	11 (31.43)	6 (21.43)	
Total	35 (100)	28 (100)	
Mean value	4.65	3.04	<0.001

Table 2 Comparison of tumor cellularity in pre and post NACT specimens

Cellularity range(%)	Pre NACT number of cases (%)	Post NACT number of cases (%)	p-value
0-10	0 (0)	7 (20)	
11-20	0 (0)	1 (2.86)	
21-30	0 (0)	4 (11.42)	
31-40	4 (11.42)	5 (14.28)	
41-50	5 (14.28)	8 (22.85)	
51-60	10 (28.57)	6 (17.14)	
61-70	9 (25.71)	0 (0)	
71-80	6 (17.14)	3 (8.57)	
81-90	1 (2.86)	1 (2.86)	
91-100	0 (0)	0 (0)	
Median cellularity	60%	50%	<0.001

In present study, the tumour cellularity was calculated as percentage of area occupied by invasive tumour cells and recorded in increments of 10%, with additional values of 1%

and 5% for minimal cellularity. The median cellularityin pre and post NACT specimens were 60% and 50% respectively and this difference was statistically significant ($p<0.001$) [Table 2].

The patients received either one of the three regimens of NACT. AC regimen (Doxorubicin, Cyclophosphamide followed by Paclitaxel) was the commonest (n=26, 74.28%), followed by CAF (Cyclophosphamide, Doxorubicin and 5-fluorouracil) for 6 (17.14%) and CEF (Cyclophosphamide, Epirubicin,5-fluorouracil) received by 3(8.58 %)cases. In our study, out of 35 cases, 10 cases received 8 cycles (28.66%), 20 cases received 6 cycles (57.14%) and 5cases received 4 cycles (14.29%) of NACT. Out of 35 cases, 7 (20%) showed complete response, 19 (54.28%) hadpartial response and 9 (25.72%) had no response [Table 3] [Fig 1]. Post NACT, out of 35, two cases were of stage IA (5.71%), 6 of stage IIA (17.14%), 9 of stage IIB (25.73%), 7 of stage IIIA (20%) and one case of stage IIIB(2.85%) and 3 of stage IIC (8.57%).

Table 3 Correlation of cycles of regimen received and pathologic response

Regimen	No of Cycles	No of cases	pCR	pPR	pNR
AC	4	1	0	1	0
	6	15	4	10	1
	8	10	1	5	4
Total	-	26	5	16	5
CAF	4	2	0	1	1
	6	4	1	0	3
	8	0	0	0	0
Total	-	6	1	1	4
CEF	4	2	1	1	0
	6	1	0	1	0
	8	0	0	0	0
Total	-	3	1	2	0

AC : Doxorubicin, Cyclophosphamide, Paclitaxel
CAF: Cyclophosphamide, Doxorubicin and 5-fluorouracil
CEF: Cyclophosphamide, Epirubicin, 5-fluorouracil
pCR: Pathologic complete response
pPR: Pathologic partial response
pNR: Pathologic no response

Table 4 Histomorphological changes in nucleus, cytoplasm, stroma and normal breast

Location	Changes	Number of cases (%)	p-value
Nuclear	Nuclear enlargement	26 (74.28)	<0.05
	Hyperchromatism	25 (71.42)	<0.05
	Increased N:C ratio	25 (71.42)	<0.05
	Prominent nucleoli	23 (65.71)	<0.05
	Karyorrhexis/karyolysis	22 (62.85)	<0.05
	Pyknosis	18 (51.42)	<0.05
	Nuclear pleomorphism	21 (60)	<0.05
Cytoplasmic	Increased eosinophilia	22 (62.8)	<0.05
	Cytoplasmic vacuoles	10 (28.57)	>0.05
	Phagocytosis	10 (28.57)	>0.05
	Giant cells	12 (34.28)	>0.05
Stromal	Collagenization	17 (48.57%)	>0.05
	Foamy Histiocytes	11 (31.42)	>0.05
	Hemosiderin laden	9 (25.71)	>0.05
	macrophages	21 (60)	< 0.05
	Necrosis	8 (22.85)	>0.05
	Angiogenesis	11 (31.42)	>0.05
	Calcification	11 (31.42)	>0.05
	Desmoplasia	23 (65.71)	<0.05
	Chronic inflammatory	9 (25.71)	>0.05
	infiltrate	24 (68.57)	<0.05
	Hyalinizationof blood vessels		
	Fibrosis		
Normal breast	Parencymal atrophy	15(42.85%)	>0.05
	Cytotoxic effects	29(82.85%)	>0.05

Table 5 Comparative details of histomorphologic changes

Location	Changes	MohanRCP *et al* [17] (2018) (%)	Sheereen S*et al* [4] (2018) (%)	Philipose CS *et al* [18] (2019) (%)	Present study (2021) (%)
Nuclear	Nuclear enlargement	-	89.7	-	74.3
	Hyperchromatism	60	87.2	-	71.4
	Increased N:C ratio	45	84.6	-	71.4
	Prominent nucleoli	-	76.9	-	65.7
	Karyorrhexis/karyolysis	-	71.8	14	62.8
	Pyknosis	-	59	16	51.4
	Nuclear pleomorphism	55	61.5	-	60
Cytoplasmic	Increased eosinophilia	-	-	-	62.8
	Cytoplasmic vacuoles	15	-	15	28.6
	Phagocytosis	-	-	-	28.6
	Giant cells	30	35.9	5	34.3
Stromal	Collagenization	-	35.9	-	48.6
	Foamy histiocytes	25	20.5	5	31.4
	Hemosiderin laden macrophages	40	17.9	5	25.7
	Necrosis	25	74.4	16	60
	Angiogenesis	-	23.1	-	22.8
	Calcification	15	23.1	-	31.4
	Desmoplasia	-	59	-	31.4
	Chronic inflammatory infiltrate	55	-	19	65.7
	Hyalinizationof blood vessels	-	5.1	17	25.7
	Fibrosis	95	64.1	5	68.7

Table 6 Comparative data on pathologic response with other studies

Response	Faneyte IF et al[14] 2003 (n=97) (%)	Sethi et al[8] 2013 (n=40) (%)	Vasudevan et al[12] 2015 (n=48) (%)	Shintia et al [20] 2016 (n=42) (%)	Mohan RCP et al[17] 2018 (n=31) (%)	Sheereen et al [4] 2018 (n=39) (%)	Savita et al [9] 2019 (n=31) (%)	Present study 2021 (N=35) (%)
pCR	3	20	27.1	4.76	9.68	17.9	16.1	20
pPR	64	37.5	70.9	59.53	54.84	15.4	58.1	54.58
pNR	33	42.5	2	35.71	35.48	66.7	25.8	25.72

Chemotherapy induced histomorphological changes were studied in detail (nuclear, cytoplasmic, stromal) inaffected [Fig2,3] as well as in adjacent normal breast [Fig 4]. Many of them show statistical significance post NACT[Table 4].

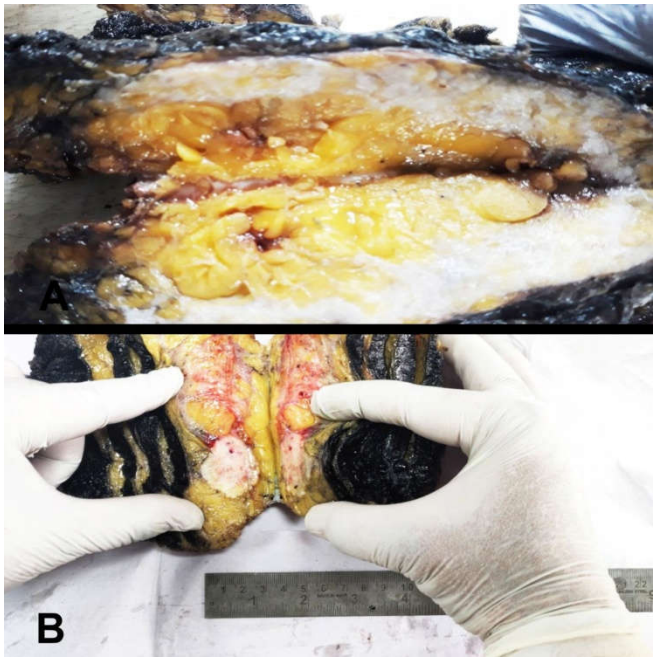

Figure 1 Post NACT MRM specimen showing (A) Only fibrosis without any residual tumour in a case ofpathological complete response, (B) Tumour in a case of pathological no response.

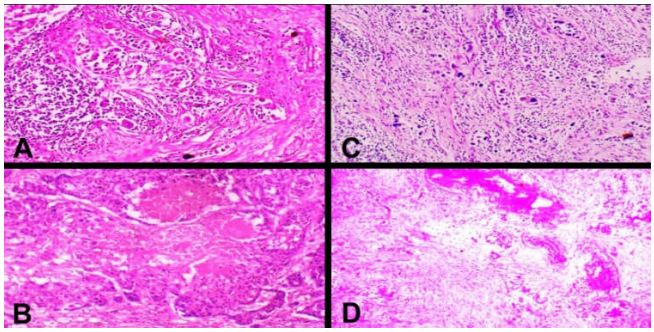

Figure 2 Photomicrographs of post NACT breast carcinoma showing (A) Nuclear hyperchromasia, inflammatoryinfiltrate, fibrosis and calcification (H&E, 100X), (B) Necrosis, inflammatory infiltrate and increased eosinophilia(H&E, 100X), (C) Dystrophic calcification, nuclear pyknosis and inflammatory cell infiltrate (H&E, 100X), (D).Complete replacement of tumour bed by fibrosis, collagen tissue and hyalinization of blood vessels (H&E, 100X).

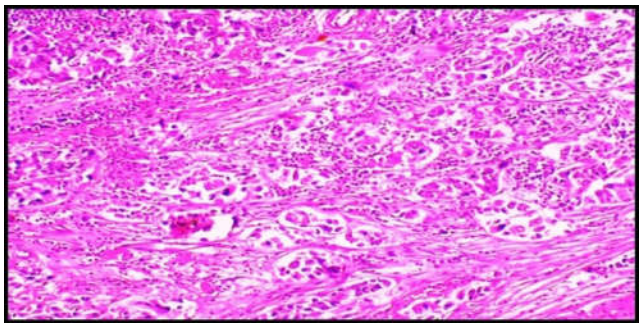

Figure 3 Photomicrograph of post NACT breast carcinoma showing tumour cells in acini and nests throughout thestroma in a case having pathological partial response (H&E, 400x).

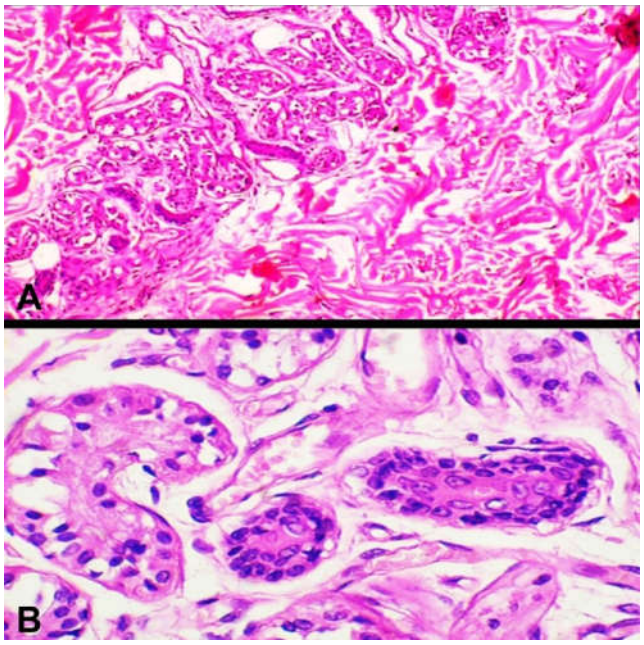

Figure 4 (A) Photomicrograph of post NACT breast carcinoma showing nuclear hyperchromasia and cytoplasmicvacuolation in adjacent breast parenchyma (H&E, 100X), (B) Photomicrograph of post NACT breast carcinomashowing nuclear hyperchromasia and cytoplasmic vacuolation in adjacent breast parenchyma (H&E, 400X).

DISCUSSION

The mean age of the patients in our study was 53.86 ±10.13 years with 5th decade being the most affected group as also reported by many other authors.[4,8,9,12] The IDC NOS was commonest carcinoma as also documented in other studies. [4,8,9,12] In present study, the mean tumour size before and after NACT was 4.65 cm and 3.04 cm respectively ($p< 0.001$) [Table 1]. The reduction in size was seen in both small and large tumours and no correlation of pathological response with reduction in size was noted. The tumour size pre and post NACT was 22.16 cm and11.74 cm respectively with 47% reduction in a study done by Sethi D *et al* [8]. Vasudevan D *et al*. [12] studied 48patients where tumour size ranged from 2.5-8cm, the mean clinical tumour size at diagnosis was 3.75 cm, with a standard deviation of 2.36. Sheereen S *et al* [4] observed the mean tumour size before chemotherapy as 3.75 cm and after chemotherapy it was 1.75 cm ($p<0.001$). Fisher ER *et al*. [13] observed that 70-80% of the patients demonstrated ≥ 50% decrease in the mean tumour size.

Stage II was commonest stage post NACT in present study (42.85%) as also observed by Sheereen S *et al*. [4](61.5%), Faneyte IF *et al*. [14] (41%) and von Minckwitz G *et al*. [15] (52%). The reduction in tumour cellularity post NACT was also comparable to other studies (Sheereen S *et al*. [4] and Pasam RK *et al*. [16]

In present study, AC regimen was the most common chemotherapy received (n=26, 74.28%). The second mostcommon regimen was CAF (6 cases, 17.14%) followed by CEF regimen (3 cases, 8.58 %). In the study of Sheereen S *et al*. [4], AC regimen was the most common (n=26, 64.1%), CAF being second most common (n=8, 20.5%) followed by CEF regimen (n=6, 15.38%). In present study, 10 cases received 8 cycles (28.66%), 20 received 6cycles (57.14%) and 5 received 4 cycles (14.29%) of NACT. Sheereen S *et al*. [4] studied 39 cases, where 27(69.2%) cases received 4 to 6 cycles, while 12 (30.7%) cases received more than 6 cycles of chemotherapy. The number of chemotherapy cycles varied from 2-6 depending on the initial tumour size to make it operable in studies done by Sethi D *et al*. [8] and Agarwal S *et al*. [9]

An elaborative assessment of the nuclear, cytoplasmic and stromal changes was done before and after the therapy inour study [Table 4] [Fig2,3]. Table 5 enlists and compares the morphologic change with other studies.[4,13,14] Sethi D *et al*. [8] observed that the collagenization and giant cell reaction were significantly correlated to pathologic response and tumour grade regression ($p<0.05$). Vasudevan D *et al*. [12] studied stromal changes such as fibrosis, elastosis, collagenization, hyalinization, microcalcification, neovascularisation, lymphocytic infiltrate and giant cell reaction of which giant cell reaction was significantly correlated to all types of tumour responses. However, none of the histomorphological findings analyzed in the post-chemotherapy specimens showed a statistically significant association with response to treatment in a study conducted by Mohan RCP *et al*. [17]

Atrophy and cytotoxic effect of NACT like hyperchromatic nuclei, high N:C ratio, cell detachment and eosinophilia were the most prominent changes in normal breast parenchyma[Fig4], as also observed by Sheereen S *et al*. [4], Sethi D *et al*. [8], Vasudevan D *et al*. [12] and Mohan RCP *et al*. [17]The response of breast carcinoma to NACT has been the focus of multiple studies, as evidenced by the number of systems that have been formulated towards this purpose. These include NSABP B18 categories, Miller Payne system, Chevallier method, Sataloff method, RCB system and AJCC 'y' classification. The present study utilized the NSABP B18 system. Table 6 narrates the comparative data on pathologic response with other studies. The variationmay be attributed partially to the different systems used for response evaluation. The studies that have used the same classification system have

given the results of pCR ranging from 3% by Faneyte IF *et al*. [14] to 15% by Chollet P *et al*. [18]

Our study was limited by having a small sample size. Also, all the tumours could not be staged pre NACT due to lack of data and hence pre and post NACT staging could not be compared to each other and pathologic response too.

CONCLUSION

NACT causes morphological alterations in the cancerous as well as the surrounding healthy tissue. For accurate gross and microscopic evaluation, an adequate clinical information regarding clinical presentation, pre-NAT location and size, biopsy/ cytological /IHC diagnosis, lymph node status, presence of calcification, NACT regimen, and clinical or radiological response should be noted. Pathologic evaluation of the tumour response is the gold standard. Post NACT staging of tumour is better predictor of survival. This ensures that the role of the pathologist is extremely important in correct diagnosis as well as grading of the tumour with a correct histopathological interpretation. It can help in an effective and planned regimen giving better prognosis and an effective patient care. Moreover, existence of several reporting systems for response assessment and lack of a standardized reporting system has limited the reproducibility and uniformity among institutions. Now a days more than ever post NACT samples are received for pathologic evaluation and this warrants the need of a standardized and reproducible system for the betterment of patients.

Conflicts of Interest

None

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