Indian Journal of Surgical Oncology (June 2023) 14(2):279–287
https://doi.org/10.1007/s13193-023-01711-1

ORIGINAL ARTICLE

Locally Advanced Breast Cancer: Response Evaluation to Neoadjuvant Chemotherapy by Clinico-Histopathological Parameters and Molecular Imaging

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Received: 25 August 2022 / Accepted: 30 January 2023 / Published online: 6 February 2023

Abstract
In India, breast cancer (BC) is not only the commonest cancer but also the commonest cause of cancer mortality among females. Advanced BC constitutes >70% of BC cases at initial presentation in India, among which locally advanced breast cancer (LABC) requires a multi-disciplinary approach with a combination of systemic and locoregional therapies. This descriptive hospital-based study was conducted over 1½ years after seeking approval from the institutional ethics committee. Fifty-five patients satisfying all the criteria of the study were enrolled. The data, thus, collected was pooled into Excel spreadsheet and analyzed using appropriate statistical tools. Most of the patients were postmenopausal, multiparous with breast lump being the commonest symptom. Mean baseline characteristics were age - 48 years, SUV max - 9.2, and Ki-67 - 17.8%. cT4 and cN2 were the commonest pre-NACT tumor and lymph node stage. Invasive ductal carcinoma was the commonest tumor type with the most common tumor grade being grade 3. Hormone receptor positivity and HER2 overexpression were seen in 33 and 17 patients respectively. Post-NACT 32 patients underwent breast-conserving surgery. Pathological complete response (pCR), i.e., ypT0N0, was seen in 13 patients (23.6%). There was slight alteration in hormone receptor status, HER2 expression and Ki-67 in the post-NACT resected tumor. pCR, which is a surrogate marker for improved clinical outcome (DFS and OS) in LABC patients, occurred more commonly in patients with pre-NACT grade 3 tumors, high Ki-67, hormone receptor-negative, and HER2 overexpressing BC (overall, in triple negative BC) but was statistically significant only with Ki-67. Post-NACT, SUV max with a cut off ≤1.5, and ΔSUV max of >80% correlated closely with pCR.

Keywords Locally advanced breast cancer · Neoadjuvant chemotherapy · Pathological complete response · Ki-67

Introduction

Breast cancer (BC) is not only the most commonest cancer among females across the globe, but also represents the leading cause of cancer deaths among females worldwide. Approximately 1.6 lakh new cases of BC are diagnosed every year in India and among them advanced BC (i.e., locally advanced breast cancer {LABC} and metastatic BC) constitutes >70% of the cases at initial presentation [1, 2].

LABC refers to stage III and inflammatory BC. It includes (in the absence of distant metastasis):

- Tumor of >5 cm with clinical regional lymphadenopathy.
- Tumor with direct extension into the chest wall and/or skin, including satellite nodule or ulcer irrespective of its size and regardless of clinical regional lymphadenopathy.
- Tumor irrespective of size with clinically fixed or matted regional lymphadenopathy or any of internal mammary, supraclavicular, or infraclavicular lymphadenopathy clinically.

In LABC, there are two major therapeutic challenges, namely control of disease and prolonging survival. Thus, LABC management requires a multi-disciplinary approach with a combination of systemic (neoadjuvant chemotherapy {NACT}) and loco regional therapies [3]. The purpose of NACT is to downstage tumor, treat micro metastasis, reduce operative morbidity including feasibility of breast-conserving surgery (BCS), and to obtain a pathological complete response (pCR) which is a surrogate marker for improved

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clinical outcome, i.e., disease-free survival (DFS) and overall survival (OS) [4].

This study would encompass clinico-histopathological parameters and molecular imaging with a view to predict response to NACT in LABC.

Methods

Approval for the study was obtained from the institutional ethical committee prior to the study. The patient selection criteria for 230 subjects screened for this study were divided as follows:

A) Inclusion criteria:

- Female patients with informed consent
- Age of ≥18 years
- LABC undergoing NACT
- ECOG performance status 0 to 2 and acceptable organ function.

B) Exclusion criteria:

- Patients with history of any other coexistent malignancy within last 5 years,
- Pregnant or breastfeeding females
- Grade ≥3 peripheral neuropathy (as per CTCAE)
- Patients with current severe uncontrolled systemic disease and concurrent serious, uncontrolled infections

Pre-NACT clinical and histopathological variables were recorded along with pre-NACT fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) findings. Post-NACT (prior to surgery) repeat FDG PET-CT findings were recorded. Surgery was either BCS or modified radical mastectomy (MRM) with regional nodal management that was based on baseline cT and cN stage, the clinical response along with the patient's preference. Complete resected specimen along with all the lymph nodes sampled were histopathologically examined for response and various other histopathological parameters which was also recorded.

The data collected was pooled in Microsoft Excel spreadsheet, and then transferred for statistical calculations to the SPSS (version 21) software. Continuous variables are expressed as mean ± standard deviation and are compared pre- and post-NACT by performing paired *t*-test. Categorical variables are presented using actual numbers and percentages and are compared by chi-square test. *p* value of <0.05 is considered statistically significant.

NACT regimen: 50 patients received anthracycline-based chemotherapy. In view of a contraindication to the steroids or infusion reaction to a taxane, 5 patients received nabpaclitaxel instead of paclitaxel/docetaxel. Among the 17 patients with HER2 overexpression, all received anti-HER2 therapy with only 3 receiving dual anti-HER2-based regimen (due to logistics). Dose dense regimen was given to 28 patients.

AJCC/UICC, BC anatomic TNM staging system of 2017 was used [5]. The status of histopathological variables was detected as per the ASCO/CAP clinical practice guidelines [6]. pCR in our study was described as "post-NACT absence of any residual invasive and/or in situ carcinoma on histopathological evaluation of complete resected specimen and all the lymph nodes sampled," i.e., ypT0 ypN0 [4]. Tumor response and size were evaluated using the RECIST 1.1 criteria and PERCIST criteria were used to assess tumor activity [7].

FDG PET-CT protocol: FDG PET scan with a diagnostic high-resolution CT scan was carried out from the vertex to mid-thigh using a dedicated PET scanner with 16 slice per second multi detector CT in patients who had fasted for at least 4 h and had a blood sugar value of ≤180mg/dl. For bowel opacification, oral contrast was administered. The non-ionic intravenous contrast injection was administered. Specific dose optimization protocols were used on CT to reduce radiation dose to the patient. A separate sequence with breath hold was performed for the lung and a delayed series was performed for the brain. A semi-quantitative analysis of FDG uptake was performed by calculating SUV value corrected for dose administered and patient's body weight.

Results

Over 1½ years of study period in the study area, 230 new cases of BC were diagnosed, of which 78 patients (33.9%) were identified with LABC of which 55 patients fulfilled all the criteria of our study.

The patient's age ranged from 31 to 62 years (mean: 48 ± 6.5 years) with majority belonging to 41 to 50 years (43.6%) age group, and only 2 patients (3.6%) were <35 years. The age at menarche ranged from 10 to 16 years (mean: 13 ± 1.6 years) and majority of the patients were postmenopausal (52.7%). The age at first child birth ranged from 18 to 29 years (mean: 21 ± 4.7 years) and majority of the patients were multiparous (81.8%). Breast lump was the commonest symptom (100%) and most of the patients presented themselves 3 to 6 months (52.7%) after the occurrence of first symptom (mean: 4.5 ± 1.8 months).

BC occurred slightly more common in the left breast (56.4%), and was predominantly located in the upper-outer quadrant (54.6%). cT4 (47.3%) and cN2 (58.2%) were the most common baseline clinical tumor and lymph node stage. Sixty percent of the patients were hormone receptor (HR)–positive (estrogen receptors {ER} or progesterone receptor {PgR} or both), 30.9% of the patients were HER2-positive, and 27.3% were triple negative BC (TNBC). Majority had invasive ductal carcinoma (IDC; 96.4%), and grade 3 (56.3%) tumor. The mean Ki-67 was 17.8 ± 6.8% and it was relatively higher in ER-negative (24.9 ± 3.3), PgR-negative (23.3 ± 4.3) BCs and grade 3 (22.5 ± 5.2) tumors. These baseline clinico-histopathological parameters are depicted in Table 1.

Post-NACT, 32 patients (58.2%) underwent BCS. In the resected specimen, pCR was seen in 13 patients (23.6%), partial response (PR) in 38 patients (69.1%), and stable disease (SD) in 4 patients (7.3%). None of the patients had disease progression (PD).

Post-NACT, the histopathological evaluation revealed (Table 2): IDC (95.2%) was the commonest histological type, 90.5% of the tumors (excluding pCR group) were downstaged with 47.6% of the patients with clinical node positive disease being rendered node negative, majority having grade 2 tumor (59.5%) and free margins (88.1%). Lymphovascular invasion (LVI), ductal carcinoma in situ (DCIS), and perinodal extension (PNE) were present in 26.2%, 23.8%, and 14.3% of the patients respectively. HR-positive, HER2-positive, and high Ki-67 (>20%) were present in 57.1%, 21.4%, and 19.1% of the patients respectively. Post-NACT, there was alteration in the ER, PgR, and HER2 expressions by 9.6%, 2.4%, and 4.8% respectively and Ki-67 by 9.5%.

pCR occurred more commonly in younger patients, postmenopausal females, smaller tumors, grade 3 tumors, high Ki-67, and HR-negative and HER2-positive BCs (overall, in TNBC). This is depicted in Table 3. Mean Ki-67 was 17.8 ± 6.8% in overall study population, 21.5 ± 6.1 in pCR group, and 16.6 ± 6.6 in non-pCR group. It was statistically significant with pCR ($p = 0.043$).

No association was found between pCR and SUV max at baseline. Post-NACT SUV max was ≤1.5 in 8 patients (61.5%) with pCR and in 12 patients (28.6%) in non-pCR group. No association was found between pCR group and non-pCR group with respect to ΔSUV max. ΔSUV max was >80% in 10 patients (76.9%) with pCR and 11 patients (26.2%) in non-pCR group. Association of various characteristics with SUV max and ΔSUV max with respect to pCR group and non-pCR groups is depicted in Table 4.

Discussion

BC is the commonest cancer among females in India with steady rise in the number [8]. Likewise, BC management also has significantly evolved over the decades significantly improving DFS and OS along with cosmetic outcomes [9].

The incidence of LABC in our study was 33.9% comparable to other Indian studies, but higher as compared to the west where majority present with early BC [10].

The mean age at presentation in our study is 48 years, similar to other Indian studies, but approximately a decade earlier than west [10]. Young BC (<35 years) constituted 3.6% of cases, that is less than other Indian study, but was similar to that in the west [11]. Loibl et al. in their study showed that age of the patient is an important, independent prognostic factor in HR-positive/HER2-negative tumors [12].

The BC occurred more commonly in the postmenopausal women in our study, comparable with other studies [10]. The mean age at menarche in our study is 13 years, comparable with other studies [13]. Orgéas et al. in their study showed that age at menarche is a significant prognostic factor while there are no significant associations with other menstrual factors [14]. In their study, it was also showed that women who were 11 years or younger at menarche had higher probability of high-grade tumors and lymph node metastases. The probability of dying within 5 years of diagnosis increased by 72% in women with early menarche [14].

According to the study by Gogia A et al. [10], BC was found slightly more in left breast which was in accordance with our study with predominance of location in the upper quadrant. Laterality of BC has shown to have no significant association with prognosis. In a study by Chang et al., it was found that better DFS is obtained with outer quadrant tumors treated with NACT in comparison to inner/both quadrant tumors [15].

cT4 is the most common baseline tumor stage in our study, comparable to other study [16]. Esserman et al. in their study found that a small tumor size was associated with a good prognosis, whereas post-NACT, a residual tumor of >2 cm was associated with higher risk of loco regional relapses [17]. cN2 was the most common baseline clinical lymph node stage in our study, comparable to other study [16]. Post-NACT, the lymph node status is of prognostic significance with respect to disease recurrence.

In our study, 60% of the patients are HR-positive, which is lower than that in west, but the proportion of patients with HER2-positive (30.9%) and TNBC (27.3%) is higher than west [18]. Such differences may be due to the racial differences and/or reduced average age at presentation. In a study by Zhou et al., it was found that HER2-positive and HR-negative patients respond better to NACT [19].

Table 1 Baseline clinico-histopathological parameters

Characteristics		*n* (%)
Age range		48 ± 6.5 years
Menarche		13 ± 1.6 years
Menopausal status	Pre- and peri-menopausal	26 (47.3)
	Postmenopausal	29 (52.7)
Age at first child birth		21 ± 4.7 years
Parity	Nulliparous	2 (3.6)
	Uniparous	8 (14.6)
	Multiparous	45 (81.8)
Symptoms of breast cancer	Breast lump	55 (100)
	Nipple retraction/distortion	23 (41.8)
	Axillary lump	11 (20)
	Pain in breast/axilla	11 (20)
	Nipple discharge	10 (18.2)
	Ulcer	9 (16.4)
	Others	17 (30.9)
Laterality	Right breast	24 (43.6)
	Left breast	31 (56.4)
Site (quadrant predominantly involved)	Upper outer	30 (54.6)
	Upper inner	08 (14.5)
	Lower outer	06 (10.9)
	Lower inner	03 (5.5)
	Central	08 (14.5)
Clinical tumor stage	T1	01 (1.8)
	T2	7 (12.7)
	T3	21 (38.2)
	T4	26 (47.3)
Clinical lymph node stage	N0	02 (3.6)
	N1	16 (29.1)
	N2	32 (58.2)
	N3	05 (9.1)
Estrogen receptor	Positive	32 (58.2)
	Negative	23 (41.8)
Progesterone receptor	Positive	26 (47.3)
	Negative	29 (52.7)
HER2/neu receptor	Positive	17 (30.9)
	Negative	38 (69.1)
Tumor histopathology	Invasive ductal carcinoma	53 (96.4)
	Invasive lobular carcinoma	2 (3.6)
Modified Bloom-Richardson grade	Grade 1	4 (7.2)
	Grade 2	20 (36.4)
	Grade 3	31 (56.3)
Ki67	>20%	22 (40)
	≤20%	33 (60)

Majority of the patients in our study had grade 3 tumor at baseline, comparable to other studies [10, 12]. In a study by Schneeweiss et al., it was found that pre-NACT tumor grade is an independent prognostic factor, with responsiveness to NACT beginning directly proportional to the grade of tumor [20].

Ki-67 is a proliferative marker and has prognostic significance in BC. In 2013, St. Gallen Consensus endorsed the use of Ki-67 in the molecular classification of BC, as Ki-67 value of >20% was found to have good concordance in differentiating luminal type A and B (luminal B is more chemo sensitive) [21]. A high Ki-67 is found to be associated with

Table 2 Post-NACT histopathological parameters of resected specimen

Characteristics		*n* (%)
Tumor Morphology	Invasive ductal carcinoma	40 (95.2)
	Invasive lobular carcinoma	2 (4.8)
Pathological tumor stage	T0	18 (32.7)
	T1	13 (23.6)
	T2	15 (27.3)
	T3	6 (10.9)
	T4	3 (5.5)
Pathological lymph node stage	N0	33 (60)
	N1	14 (25.5)
	N2	5 (9.1)
	N3	3 (5.4)
Modified Bloom-Richardson grade	1	9 (21.4)
	2	25 (59.5)
	3	8 (19.1)
Estrogen receptor	Positive	24 (57.1)
	Negative	18 (42.9)
Progesterone receptor	Positive	23 (54.8)
	Negative	19 (45.2)
HER2/neu receptor	Positive	9 (21.4)
	Negative	33 (78.6)
Ki67	>20%	8 (19.1)
	≤20%	34 (80.9)
Margin	Free	38 (90.5)
	Close	4 (9.5)
	Positive	0 (0)
Ductal carcinoma in situ	Positive	10 (23.8)
	Negative	32 (76.2)
Lymphovascular invasion	Positive	11 (26.2)
	Negative	31 (73.8)
Perinodal extension	Positive	6 (14.3)
	Negative	36 (85.7)

In this table for each characteristic/variable n=42, as 13 patients had pCR except for tumor and node where n=55

good response to NACT and pCR in various studies, but there is no validated value to differentiate high and low Ki-67 with various cut-offs being used in various studies, like 12% by Nishimura et al., 20% by Li et al., and 25% by Kwan II Kim et al. [22].

Post-NACT, 32 patients (58.2%) underwent BCS. The rate of BCS post-NACT varied across studies from 40% to 85% [23]. This wide variation could be due to the difference in the study population and different NACT regimens used, including surgeon decision and patient's preferences.

Post-NACT, pCR was seen in 13 patients (23.6%), PR in 38 patients (69.1%), and SD in 4 patients (7.3%). The rate of pCR varied widely from 13 to 65% in various studies, but its rate in our study was comparable to that in two biggest trials of NACT [4, 22]. Such wide variation in pCR rate may be due to the disparity of pCR definition used in different studies along with variation in BC subtypes and the nature of NACT regimen used.

Post-NACT, the histopathological evaluation is discussed in the current paragraph. IDC (95.2%) was identified as the commonest type in our study and all patients who achieved pCR were from this group only. This was comparable to other studies which showed that IDC is more responsive to chemotherapy [24]. The overall response rate (ORR) was 92.7% and excluding the pCR group, 90.5% of the patient's tumors were downstaged and 47.6% of the clinical node positive disease patients were rendered node negative. The group of patients who were rendered node negative was expected to do better next to the pCR group. It is also seen that the patients who were rendered node negative may harbor occult metastasis (~16%), but this will not affect either OS or DFS. Though majority had grade 3 tumor pre-NACT, grade 2 was predominant post-NACT tumor grade suggesting downgrading of tumor and this was comparable with another study [25]. Majority had free margins and 9.5% of patients had close (≤2 mm) and non had positive margins. The rate of positive margin in various studies shows great variability (5 to 39.8%) and has shown to increase the risk of local recurrence, but a close margin (BCS followed by radiation) does not increase the risk of local recurrences. DCIS and LVI were present in 23.8% and 26.2% of the patients respectively, which was slightly less compared to other studies and their presence is associated with chemoresistance [24]. PNE was present in 14.3% cases which was comparable with another study and is associated with poor DFS [26].

In our study, we found alteration in the ER, PgR, and HER2 status by 9.6%, 2.4%, and 4.8% respectively and Ki-67 by 9.5%. This alteration was slightly less compared to other studies and may be due to intra-tumoral heterogeneity, intra- and inter-observer variability, and preferential killing of certain subclones of tumor cells by NACT [27]. Current guidelines do not recommend repeat performance of these markers on resected tumor. As notable alterations were seen, although not statistically significant, it may justify the re-evaluation of these IHC markers in the post-NACT specimen as these have a significant role in the management.

pCR was achieved in 13 patients (23.6%) in our study and occurred more commonly in patients with grade 3 tumors, high Ki-67, HR-negative and HER2-positive BCs (overall, in TNBC), but showed statistically significant correlation only with Ki-67.

pCR was found more commonly in younger patients in our study comparable to other studies [28, 29]. pCR was found slightly more common among postmenopausal patients in our study which was in contrast to other studies where it was more commonly in premenopausal patients [28, 29]. pCR was found more commonly in smaller tumors in

Table 3 Univariate associations of baseline clinico-histopathological parameters with pCR

Characteristics	Total patients *n*=55 (%)	pCR *n*=13 (%)	Non-pCR *n*=42 (%)	*p* value
Age (years)				
≤ 50	36 (65.4)	11 (30.5)	25 (69.5)	0.179
> 50	19 (34.6)	2 (10.5)	17 (89.5)	
Menopausal status				
Pre- and peri-menopausal	26 (47.3)	6 (23.1)	20 (76.9)	0.942
Postmenopausal	29 (52.7)	7 (24.1)	22 (75.9)	
Clinical tumor stage				
T1–3	29 (52.7)	7 (24.1)	22 (75.9)	0.942
T4	26 (47.3)	6 (23.1)	20 (76.9)	
Clinical lymph node stage				
N0–1	18 (32.7)	5 (27.8)	13 (72.2)	0.694
N2–3	37 (67.3)	8 (21.6)	29 (78.4)	
Modified Bloom-Richardson grade				
Grade 1–2	24 (43.7)	3 (12.5)	21 (87.5)	0.173
Grade 3	31 (56.3)	10 (32.3)	21 (67.7)	
Estrogen receptor				
Negative	23 (41.8)	9 (39.1)	14 (60.9)	0.075
Positive	32 (58.2)	4 (12.5)	28 (87.5)	
Progesterone receptor				
Negative	29 (52.7)	9 (31.0)	20 (69.0)	0.281
Positive	26 (47.3)	4 (15.4)	22 (84.6)	
HER2/neu receptor				
Negative	38 (69.1)	10 (26.3)	28 (73.7)	0.577
Positive	17 (30.9)	3 (17.7)	14 (82.3)	
Ki67				
≤ 20%	34 (61.8)	4 (11.8)	30 (88.2)	0.043
> 20%	21 (38.2)	9 (42.9)	12 (57.1)	
Hormone receptor (HR) and HER2/neu receptor (HER) status				
HR positive, HER negative	23 (41.8)	4 (17.4)	19 (82.6)	0.511
HR positive, HER positive	10 (18.2)	1 (10.0)	9 (90.0)	
HR negative, HER positive	7 (12.7)	2 (28.6)	5 (71.4)	
HR negative, HER negative	15 (27.3)	6 (40.0)	9 (60.0)	

our study comparable to other studies [28, 29]. pCR showed no relation with clinical node status in our study in contrast to being more common in patients with clinical negative node status. This might be as cN0 patients were very less in our study. pCR was found more commonly in grade 3 tumors in our study comparable to other studies [30]. pCR was found more commonly in ER-negative, PgR-negative, and HER2-positive BCs in our study comparable to other studies [28, 30]. pCR was found more commonly in tumors with high Ki-67 (>20%) in our study comparable to other studies [31]. The mean Ki-67 in our study was 17.8 ± 6.8%. It was more in tumors of pCR group (21.5 ± 6.1%) in comparison with tumors of non-pCR group (16.6 ± 6.6). Based on HR and HER2 status, we classified our patients into 4 groups and pCR was more common in TNBCs, comparable to other studies [31].

SUV max is a prognostic marker in BC and a sequential SUV max during NACT can help assess response to NACT [32]. The sensitivity and specificity of FDG PET-CT in evaluation of response to NACT varied widely across studies from 39 to 100% and 74 to 100% respectively [33]. This wide variation might be due to different patient population, different timings of the sequential scan with respect to NACT, and different PET-CT protocols with different SUV cut-offs and different pathological response criteria used in various studies. In our study, no association between pCR and SUV max was observed at baseline, in contrast to other studies where various biological parameters showed correlation with SUV max [34]. However, post-NACT SUV max (≤1.5) in our study correlated closely with pCR, but was not statistically significant. Post-NACT SUV max was ≤1.5 in 8 patients (61.5%) with pCR and in 12 patients (28.6%) of non-pCR group. No association was

Table 4 Univariate association of baseline histopathological parameters with SUV max and ΔSUV max in pCR

Characteristics	Total patients *n*=55 (%)	Pre-NACT mean SUV max (*n*=55)	Post-NACT mean SUV max in pCR (*n*=13)	Post-NACT mean SUV max in non-pCR (*n*=42)	*p* value	ΔSUV max in pCR (*n*=13)	ΔSUV max in non-pCR (*n*=42)	*p* value
Clinical tumor stage								
T1–3	29 (52.7)	6.1 ± 1.6	1.3 ± 0.7	2.5 ± 1.1	0.542	78.3 ± 26.4	67.2 ± 18.8	0.533
T4	26 (47.3)	12.7 ± 1.9	1.2 ± 0.7	2.0 ± 0.9		85.5 ± 25.7	63.4 ± 21.5	
Clinical lymph node stage								
N0–1	18 (32.7)	8.8 ± 3.9	1.5 ± 0.5	2.2 ± 1.1	0.778	76.6 ± 31.5	71.2 ± 20.2	0.326
N2–3	37 (67.3)	9.4 ± 3.6	1.1 ± 0.7	2.3 ± 1.0		84.9 ± 21.9	62.7 ± 19.6	
Modified Bloom-Richardson grade								
Grade 1–2	24 (43.7)	9.3 ± 3.6	1.3 ± 0.8	2.3 ± 0.9	0.993	84.3 ± 04.7	66.8 ± 21.6	0.989
Grade 3	31 (56.3)	9.2 ± 3.9	1.3 ± 0.7	2.3 ± 1.1		80.9 ± 29.9	63.9 ± 18.6	
Estrogen receptor								
Negative	23 (41.8)	9.1 ± 3.8	1.3 ± 0.7	2.3 ± 0.9	0.891	75.7 ± 26.9	61.8 ± 17.9	0.536
Positive	32 (58.2)	9.3 ± 3.7	1.1 ± 0.7	2.3 ± 1.1		95.0 ± 18.9	67.1 ± 21.0	
Progesterone receptor								
Negative	29 (52.7)	9.0 ± 3.8	1.3 ± 0.7	2.2 ± 1.1	0.878	75.7 ± 26.9	62.8 ± 18.3	0.515
Positive	26 (47.3)	9.4 ± 3.7	1.1 ± 0.7	2.3 ± 1.0		95.0 ± 18.9	67.7 ± 21.5	
HER2/neu receptor								
Negative	38 (69.1)	9.6 ± 3.9	1.1 ± 0.7	2.3 ± 0.9	0.626	83.9 ± 26.2	64.6 ± 20.5	0.493
Positive	17 (30.9)	8.4 ± 3.2	1.8 ± 0.5	2.3 ± 1.3		73.9 ± 25.1	66.9 ± 19.3	
Hormone receptor (HR) and HER2/neu receptor (HER) status								
HR positive, HER negative	23 (41.8)	9.4 ± 3.8	1.1 ± 0.8	2.3 ± 1.0	0.801	95.0 ± 18.9	67.1 ± 22.3	0.657
HR positive, HER positive	10 (18.2)	9.2 ± 3.4	1.1 ± 0.0	2.1 ± 1.3		81.7 ± 00.0	67.2 ± 17.9	
HR negative, HER positive	7 (12.7)	7.4 ± 2.4	2.2 ± 0.2	2.7 ± 1.2		70.1 ± 30.1	66.2 ± 21.7	
HR negative, HER negative	15 (27.3)	9.8 ± 4.2	1.1 ± 0.6	2.1 ± 0.7		76.6 ± 27.8	59.3 ± 14.8	

found between ΔSUV max with between pCR group and non-pCR group in our study, but ΔSUV max (>80%) correlated closely with pCR, but was not statistically significant. ΔSUV max was >80% in 10 patients (76.9%) with pCR and in 11 patients (26.2%) of non-pCR group. Previous studies suggest that ΔSUV max after the initial first and/or second cycle of NACT can predict the response to NACT [35].

The main limitations of our observational study are that it was carried out in a single hospital with a small sample size and with even smaller subgroups with no follow-up or control arm and no single standardized NACT regimen. FDG PET-CT was repeated only after completion of NACT with no intervening scans.

Conclusion

The prevalence of advanced BC is greater in India, with BC occurring about a decade earlier in their most productive years of life then in the west with larger proportion of patients being HER2-positive or TNBC. In our study, ORR was 92.7% with pCR being achieved in 23.6% of the patients. Excluding patients who achieved pCR, 90.5% of the tumors were downstaged and 47.6% of the clinical node positive disease patients were rendered node negative; thus, NACT is the initial treatment of choice in LABC involving multi-disciplinary approach with its

added advantages. Post-NACT, there was slight alteration in IHC markers. pCR, which is a surrogate marker for improved OS and DFS, occurred more commonly in patients with grade 3 tumor, high Ki-67, HR-negative and HER2-positive tumors (overall in TNBC) but was statistically significant only with Ki-67. Post-NACT, SUV max with a cut off ≤1.5 and ΔSUV max of >80% correlated closely with pCR.

Declarations

Conflict of Interest The author declares no competing interests.

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