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Breast Cancer

Clinicopathological Evaluation of Patients with Hormone Receptor–Positive HER2-Negative Metastatic Breast Cancer Progressing on Endocrine Treatment: A Real-World Retrospective Study from a Regional Cancer Center

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Abstract


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Metastatic breast cancer (MBC) is an incurable disease with the primary aim of treatment being the improvement of the patient's quality of life and the delay of disease progression. A substantial proportion of patients with hormone receptor (HR)-positive MBC eventually experience progression despite endocrine treatment. As endocrine resistance remains a significant challenge, we aim to comprehend the intricate relationship between clinicopathological characteristics and the utility of various parameters as predictive markers for hormonal treatment response. This study, conducted at a single center, is ambispective in nature and includes hormone receptor (HR)-positive, human epidermal growth factor 2–negative MBC patients who progressed while on endocrine treatment, selected through purposeful sampling. Nominal data were analyzed in terms of frequency distribution, and continuous variables were represented as median/mean ± standard deviation. Spearman's correlation test and chi-square test were employed to examine variable dependencies. Data comparisons were performed using the independent t-test, one-way analysis of variance, or Mann–Whitney's test. The majority of our study participants ($n = 44$, 64.70%) presented with de novo metastasis, while the remainder ($n = 24$, 35.29%) were patients who progressed from early-stage breast cancer to metastasis. The overall mean age of our study population at presentation was 47 ± 11 years. Patients with upfront stage 4 tumors presented at an older age, exhibited grade 2 tumors, had a higher frequency of bone-only metastasis, and experienced longer progression-free survival (PFS) compared to patients who progressed from the early stage to metastasis. Multiple visceral involvements had a significant negative impact on PFS in contrast to cases with single visceral or bone-only involvement. No significant associations with PFS were observed for the Ki-67 index, first-line chemotherapy, or endocrine therapy. The extent of metastasis to

Keywords

- hormone receptor-positive metastatic breast cancer
- progression
- PFS (progression-free survival)

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various organs emerged as the most influential factor in determining PFS. Consequently, we propose the necessity for larger prospective studies aimed at identifying superior or additional biomarkers.

Introduction

Female breast cancer being the most common cancer globally contributes to 11.7% of all reported cancers worldwide surpassing lung cancer too.[1] According to GLOBOCAN 2020 data, in India alone, breast cancer accounted for 13.5% of all cancers and 10.6% of all cancer-related deaths.[2] It is not surprising that majority of patients in low socioeconomic countries present in advanced stage, owing to lack of awareness. Though breast cancer has a better prognosis compared with other aggressive cancers, the 5-year overall survival decreases from 99% for localized disease to 27% for distant metastasis.[3]

Breast cancer is a heterogeneous disease and its effective management takes into consideration several factors related to the patient, the stage of the disease and prognostic and predictive factors, which also include the hormone receptor (HR) and human epidermal growth factor 2 (HER2)-neu status. Breast cancers that express these receptors are amenable to targeted therapy and those which do not express any of these receptors are called triple-negative breast cancers, which are treated with traditional chemotherapeutic agents. Estrogen and progesterone receptors (ER and PR) are expressed in ~85% of breast cancers, and this proportion increases with age.[4]

Endocrine therapy constitutes the mainstay of treatment in advanced HR-positive breast cancer, alone or in combination with chemotherapy. Though most patients respond initially, the endocrine therapy eventually fails due to intrinsic and acquired resistance to antihormonal therapy.[5–8] About 30 to 40% metastatic breast cancer (MBC) patients do not respond to hormonal treatment from the outset due to intrinsic resistance, while acquired resistance has been observed in ~20 to 30% of MBCs who responded initially.[5,9] This is due to ER-independent escape pathways that may render cells resistant to treatment.[10]

Expression of ER and PR has been traditionally evaluated as clinical indicators of endocrine responsiveness.[11,12] Another commonly studied biomarker in breast cancer management is Ki-67, which is widely accepted as a proliferative index of tumor. However, clinical utility of Ki-67 assessment to guide therapeutic decisions of adjuvant or neoadjuvant chemotherapy in breast cancer is controversial.[13]

Various studies have evaluated clinicopathologic characteristics and treatment outcomes in patients with MBC, irrespective of their biomarker status. However, there is paucity of studies on endocrine-resistant MBCs from an Indian cohort. Understanding the complex association of various clinicopathological parameters could help pinpoint new treatment targets and shed light on the possible mechanisms underlying the endocrine resistance in MBCs.

Subjects and Methods

Study Design

This is descriptive study of 3 years duration conducted in an ambispective manner, from January 2020 to December 2022. Purposive sampling method was used for collection of MBC patients. The study began with inclusion of HR-positive and HER2-negative breast cancer patients ($n = 1{,}293$) from pathology departmental immunohistochemistry (IHC) records. Case files of these patients were reviewed for details on metastasis and treatment. Parallelly cases fulfilling the inclusion criteria were referred from medical oncology department. Consecutive patients were recruited without any selection bias. There were 92 cases of de novo metastatic breast cancer (dMBC) who presented upfront with metastasis; and 94 cases of recurrent metastatic breast cancer (rMBC) patients who progressed from early stage (stages 1–3) breast cancer to metastatic disease. The final study population comprised 68 patients (44 patients of dMBC and 24 cases of rMBC) who progressed on hormonal treatment.

Ethical Approval

The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Declaration of Helsinki of 1975, as revised in 2000. The Institutional Ethics Committee approved the study. Written informed consent was obtained from the patients before enrollment for the study.

Histopathology and Immunohistochemistry

The baseline tumor-related characteristics included morphologic type, histologic grade according to the modified Bloom–Richardson score, type of specimen for diagnosis (needle core biopsy/excised specimen; primary/metastatic sites). For rMBC, pTNM stage and histologic grade at diagnosis were recorded.

IHC was performed on an automated slide processing system (BenchMark* XT, Ventana Medical Systems, Inc., Tucson, Arizona, United States). Secondary antibodies used were SP1, 1E2, 4B5, and SP6 clones (Ventana Medical Systems, Inc.) for ER, PR, HER2, and Ki-67, respectively. IHC analysis was done in compliance with recommendations of American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2013/2018 update.[14,15] Allred scoring system was adopted for evaluation of ER, PR, and HER2 status. With regard to HER2 status, scores of 0 and 1+ were considered negative, 2+ as equivocal, and 3+ as positive. Patients with equivocal HER2 results were further subjected for fluorescent in situ hybridization (FISH) using ERBB2/

CCP17 FISH probe kit, and positive or negative status was assigned based on ASCO/CAP 2013 HER2 testing guidelines.[15]

Clinical Assessment

The recorded data included date of diagnosis, age and menopausal status at diagnosis, laterality, sites of distant metastasis based on contrast-enhanced computed tomography (CT)/positron emission tomography–CT/bone scans, and treatment details—type of treatment, date of commencement, and date of change in treatment. Progression of the disease was assessed based on the response evaluation criteria in solid tumors on radiological imaging studies.[16]

Statistical Analysis

Statistics was performed using GraphPad Prism statistical analysis tool (V 9.0). All the nominal data were analyzed as frequency of distribution. ER and PR expression were coded as low (grade ≤ 3), medium (grades 4–6), and high (grade 7 or higher). Ki-67 expression was coded as low ($\leq$ 12% expression), medium (13–24%), and high (>24%) based on the interquartile ranges. For determining if age had a significant impact on other variable, age was categorized into two groups: ≤ 47 and > 47 years, based on mean value.

Progression-free survival (PFS) was defined as time from start of hormone therapy (HT) to the first clinical evidence of progression for dMBC irrespective of prior exposure to chemotherapy; the same definition was applied for rMBC but prospective to development of metastasis. For dMBC cases, PFS was divided into three groups: endocrine resistant (< 12 months) and endocrine sensitive (> 12 months) for further analysis.

Spearman's correlation matrix was used to determine correlation between all the nominal variables. For comparison of two or more nominal variables, chi-square test was used. For contingency tables with value less than 40, Yates' correction was used. A p-value of < 0.05 was considered as cutoff for significance.

The continuous data were analyzed with mean and standard deviation. The continuous data were also checked for presence of significant outliers using ROUT analysis ($Q = 1\%$) as described previously.[17] Upon detection of an outlier, the data point was removed from further analysis.

The normality of the data was assessed using Shapiro–Wilk's test. For normal data, comparison was performed using independent t-test or one-way analysis of variance. For all other distribution, data were analyzed using Mann–Whitney's test or Kruskal–Wallis' test. Multiple comparison following significance with Kruskal–Wallis' test was done using Dunn's multiple comparison test.

Results

Clinical Presentation

Of the total 68 cases enrolled in the study, majority were dMBC ($n = 44$, 64.70%) and the remaining 24 cases were rMBC (35.29%). The overall mean age of presentation was 47 ± 11 years (range: 24–70). ►Table 1 depicts the summary of the frequency distribution of all the variables. Based on the immunohistochemistry profile of ER, PR, HER2, and Ki-67, 63.23% of cases were assigned as luminal-A type, and 30.88% were luminal-B type. The numerical summary of age, PFS, and percentage of cells expressing Ki-67 is shown in ►Table 2.

Clinical Treatment History

Of the 44 dMBC cases, 19 patients underwent breast surgery (12 modified radical mastectomy, 2 breast conservative surgery with axillary lymph node dissection, and 5 palliative mastectomy). Six patients underwent bilateral salpingo-oophorectomy all of which had metastatic deposit. As a first-line medical treatment, 20 patients (45%) received chemotherapy and 24 patients (55%) received hormonal therapy—tamoxifen for 5 patients and aromatase inhibitors (AIs) for 19 patients.

Of the 24 cases of rMBC, 11 (45.83%) patients had received complete treatment following their initial diagnosis of early breast cancer and 13 (54.17%) patients had defaulted adjuvant treatment. Out of the former 11 patients who completed adjuvant chemotherapy and radiotherapy following surgery, tamoxifen was administered to 8 patients and AI to 3 patients in the adjuvant setting. Subsequent to metastasis, progression occurred in 21 patients on AIs, 2 patients on fulvestrant, and 1 patient on tamoxifen.

Progression-Free Survival

The PFS ranged from 4 to 32 months (mean 13 ± 7.9). There was no correlation of PFS with age, laterality, menopausal status, or expression profile of ER, PR, or Ki-67 (►Fig. 1a). A multiple linear regression analysis using ER, PR, and Ki-67 yielded no significant result (►Fig. 1b). Further, PFS was not different between age, laterality, menopausal status, molecular class, or expression profile of ER, PR, or Ki-67.

Among 44 dMBC patients, 25 patients had PFS less than 12 months and 19 patients developed progressive disease after 12 months.

To further delineate effect of ER-dependent PR expression on PFS, we compared the differences in PFS by PR expression given a high expression of ER (Allred score of 6–8). It was noted that the PFS was longer in patients with higher PR expression (Allred PR score of > 5; PFS 14 ± 8.1) compared with those with low PR expression (Allred score ≤ 5; PFS 10 ± 5.8).

Interestingly, we observed a significant difference in PFS depending on the extent of organ involvement. Though there was no significant difference between bone-only and single-visceral involvements, a significant difference was observed between bone-only and multiple visceral involvements ($p = 0.04$); single and multiple visceral involvements ($p = 0.002$) (►Fig. 2a). A heatmap of the metastatic spread between various organs is shown in ►Fig. 2b. Additionally, it was observed that previous exposure to chemotherapy or HT (both in the adjuvant and palliative setting) had no significant effect on PFS (►Fig. 3).

Correlation between Other Parameters

An overall Spearman's correlation analysis of all parameters indicated that there was a positive correlation between

Table 1 Frequency distribution of clinicopathological factors observed in the study

Parameter	Description	Number of cases	Frequency (%)
Laterality	Right	29	42.65
	Left	28	41.18
	B/L	11	16.18
Menopausal status	Premenopausal	15	22.06
	Postmenopausal	53	77.94
Morphology	Invasive ductal carcinoma—nonspecial type	58	85.29
	Invasive ductal carcinoma—special type	5	7.35
	Invasive lobular carcinoma	5	7.35
Grade	Grade 1	1	1.47
	Grade 2	50	73.53
	Grade 3	15	22.06
	Data not available	2	2.94
Stage at the time of first presentation	Stage 2	10	14.71
	Stage 3	14	20.59
	Stage 4	44	64.71
Estrogen receptor expression	Low (grade < 3)	2	3
	Medium (grades 4–6)	14	21
	High (grade 7–8)	52	76
Progesterone receptor expression	Low (grade < 3)	12	18
	Medium (grades 4–6)	29	43
	High (grade 7–8)	27	40

Table 2 Numerical summary of age, progression-free survival, and percentage of cells expressing Ki-67

	Age ($n = 68$)	Ki-67 (% expression) ($n = 64$)	Progression-free survival ($n = 68$)
Range	24–70	5–80	4–36 mo
Mean ± SD	47 ± 11	25 ± 17	13 ± 7.9
95% CI	44–50	21–29	11–14

Abbreviations: CI, confidence interval; SD, standard deviation.

coefficients—age and menopausal status ($p = < 0.01$); ER grade and PR grade ($p < 0.001$), Ki-67 and molecular class ($p = < 0.001$), and a negative correlation between stage at initial diagnosis and grade ($p = 0.01$); laterality and molecular class ($p = 0.011$) (►Fig. 1a).

Comparison of rMBC and dMBC

rMBC and dMBC are clinically different, and thus, the two groups were analyzed against each other to determine if any variables were associated with them. Of the multiple parameters analyzed (►Table 3), we determined that grade 2 was more commonly associated with dMBC, and grade 3 was more aligned with rMBC. We observed that patients with rMBC had a lower age (44 ± 12; 95% confidence interval [CI]: 39.2–48.8) compared with dMBC (49 ± 10; 95% CI: 46–52) at the time of metastatic presentation, which was nearly significant ($p = 0.06$). Additionally, rMBC had a marginally shorter PFS (11 ± 6.2 months; 95% CI: 8.52–13.5) in comparison to dMBC (13 ± 7.9 months; 95% CI: 10.7–15.3) but was not statistically different ($p = 0.37$).

Discussion

MBC is a complex disease with varied outcome based on several genetic and environmental factors. The clinicopathological features of MBC can vary depending on the location and extent of metastasis, as well as the molecular subtype of the primary breast tumor. Endocrine therapy has been the standard treatment for HR-positive MBC. However, not all patients respond to, or benefit from endocrine therapy, and a subset of patients who initially respond will eventually develop endocrine treatment resistance.[7,10] Endocrine treatment resistance in HR-positive MBC is a complex and heterogeneous phenomenon, and therefore understanding its

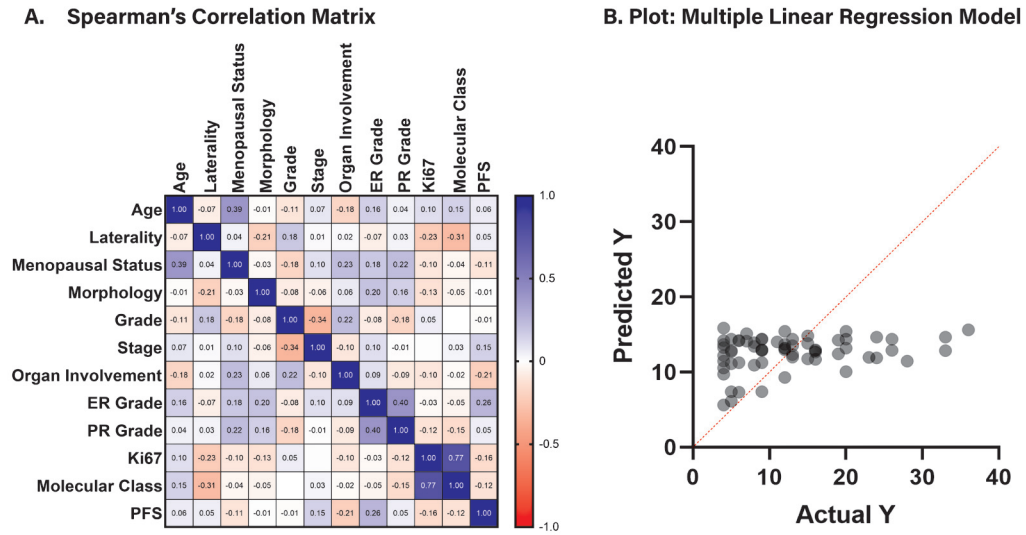

Fig. 1 (**a**) Spearman's correlation matrix showing, the *r* value between multiple variables analyzed in the study. The color scale represents *r* value (−1 to +1). (**b**) Multiple linear regression analysis using ER, PR, and Ki-67 expression to determine PFS. ER, estrogen receptor; PFS, progression-free survival; PR, progesterone receptor.

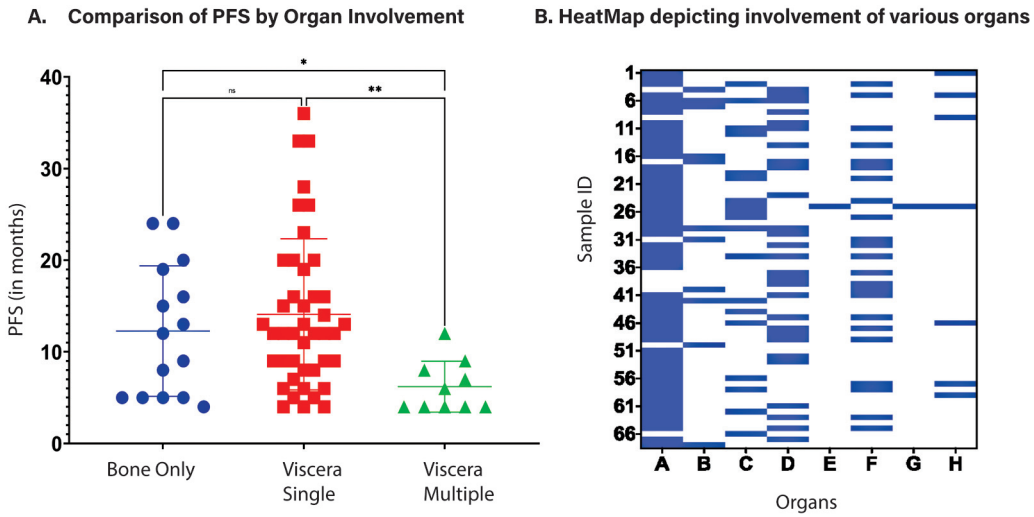

Fig. 2 (**a**) Differences in progression-free survival (PFS) depending on extent of metastasis to various organs. Plot shows mean and standard deviation. (**b**) Heatmap of various organ involvement in the examined cases. The numbers on *Y*-axis represents individual case number. The *X*-axis represents the organ involvement as follows: A—bone; B—ovaries; C—liver; D—lung; E—adrenal glands; F—distant lymph nodes; G—bone marrow; H—brain.

clinicopathological features is essential for developing effective therapeutic strategies and predicting outcomes.[8,18,19] Though several international studies have investigated the molecular and clinicopathological aspects of HR-positive and HER2-negative MBCs, there is a lacunae of equivalent studies from the Indian cohort.

Majority of MBC patients in Western countries will have a history of early breast cancer and de novo metastatic presentation is less common.[20] On the contrary, we encountered almost equal proportions of dMBC (49.19%) and rMBC (50.8%) patients. However, in the final study population of the progressed cases, dMBC (64.70%) outnumbered rMBC (35.29%) cases.

As expected, there was a significantly strong correlation between age and menopausal status. More than two-third of cases were postmenopausal, which concur with previous findings suggesting that the overall incidence of MBC is higher in older women due to their more significant risk of developing breast cancer.[21] An overwhelmingly large proportion of cases presented with invasive ductal carcinoma followed by invasive lobular carcinoma consistent with earlier studies.[22]

Age is considered as a vital factor in the development and prognosis of MBC. The overall incidence of MBC is higher in older women due to their more significant risk of developing breast cancer.[23] In a study of 14,403 women by Frank et al,[24] younger patients were found to have a significantly more aggressive presentation than older women. Though several studies have suggested a difference in risk based on age, we did not find any significant correlation between age and

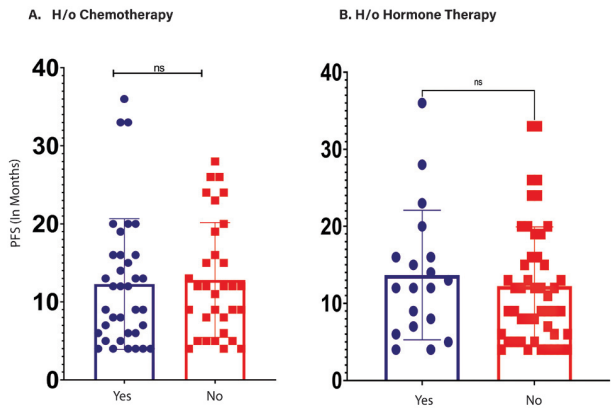

Fig. 3 Differences in progression-free survival (PFS) of cases in recurrent metastatic breast cancer with and without history of (**a**) chemotherapy and (**b**) hormone therapy. "Yes" indicates previous history of therapy and "No" indicates no history of therapy. "ns" indicates statistically not significant. *Y*-axis shows PFS (in months).

other clinical parameters. Further, our data suggested that the rMBC was seen in a younger age group (44 ± 12 years), whereas the dMBC had a higher age group (49 ± 10 years). Interestingly, we observed a negative correlation between stage and grade, which can be viewed as grade 2 breast cancer being significantly higher in dMBC patients than rMBC patients who had more commonly grade 3 tumors. These findings suggest that younger women with MBC tend to have more aggressive outcomes than older women, which has been noted in previous studies.[21,24,25]

We observed a significant correlation between luminal type and laterality, suggesting that the right breast was more commonly associated with luminal type B, similar to previously reported findings by Cheng et al.[26] In general, luminal A breast cancers have lower proliferation rates, are typically associated with an excellent response to endocrine therapy, and often have better overall survival. In contrast, luminal B breast cancers have higher proliferation rates and may

Table 3 Comparison of various clinicopathological parameters in recurrent and de novo MBC

Parameter	Description	Recurrent MBC		De novo MBC		Statistical significance *p*-Value
		Number	Frequency	Number	Frequency	
Laterality	Right	11	16.18	18	26.47	0.204
	Left	7	10.29	21	30.88	
	B/L	6	8.82	5	7.35	
Menopausal status	Premenopausal	6	8.82	9	13.24	0.665
	Postmenopausal	18	26.47	35	51.47	
Morphology	Invasive ductal carcinoma—nonspecial type	20	29.41	38	55.88	0.393
	Invasive ductal carcinoma—special type	3	4.41	2	2.94	
	Invasive lobular carcinoma	1	1.47	4	5.88	
Grade	Grade 1	–	–	1	1.47	**0.023**
	Grade 2	14	20.59	36	52.94	
	Grade 3	9	13.24	6	8.82	
Metastatic sites before progression	Bone only	5	7.35	10	14.71	0.203
	Vicera single	13	19.12	30	44.12	
	Vicera multiple	6	8.82	4	5.88	
Estrogen receptor expression	Low (grade < 3)	–	–	2	2.94	0.486
	Medium (grades 4–6)	7	10.29	7	10.29	
	High (grade > 7)	17	25.00	35	51.47	
Progesterone receptor expression	Low (grade < 3)	4	5.88	8	11.76	0.968
	Medium (grades 4–6)	10	14.71	19	27.94	
	High (grade > 7)	10	14.71	17	25.00	
Ki-67 expression	Low (< 12%)	6	8.82	7	10.29	0.320
	Medium (12–24%)	4	5.88	15	22.06	
	High > 24%	11	16.18	21	30.88	
PFS	–	$n = 24$ 11 ± 6.2	35.29	$n = 44$ 13 ± 7.9	64.70	0.3720

Abbreviations: MBC, metastatic breast cancer; PFS, progression-free survival.

exhibit more aggressive features.[27] Considered together these findings suggest that right breast cancer tends to be more aggressive.

Correlation between Progression-Free Survival and Other Variables

PFS is a highly valued clinical outcome marker, being considered as a surrogate end point in advanced breast cancers.[28] In this study, PFS was mainly influenced by the extent of metastasis. Those cases with only bone or single visceral organ involvement had a delayed PFS than patients with multiple visceral organs (►Fig. 2a). Organs that were commonly involved in the metastasis included bone, lung, liver, lymph nodes, and brain, similar to previous findings.[29] PFS was marginally longer in patients treated with AIs (13 ± 8.1) than those who were treated with tamoxifen (10 ± 6.4). We did not find any influence of age, laterality, and menopausal status on PFS. Further, we found no difference in PFS attributable to previous chemotherapy or HT exposure.

The current study showed bone as the most frequently involved site of metastasis, followed by lung, distant lymph nodes, liver, ovary, and other organs. Bone metastasis is a common complication of advanced stage of breast cancer reported to occur in more than 70% of patients with MBC. Breast cancer cells have a propensity to metastasize to bone due to the complex interactions between tumor cells and the bone microenvironment.[30]

Correlation between Progression-Free Survival and ER/PR/Ki-67

Though ER and PR expression is traditionally considered good marker to predict response to endocrine therapy, it has been increasingly identified that multiple genes and various pathways influence the outcome.[18] PR, which is largely regulated by estrogen signaling via ER, is considered as a classical molecular marker of ER activity.[7] Although PR is dependent on ER, majority of patients treated with hormonal therapy may have PR loss which could possibly be linked with innate endocrine resistance.[5] On comparison of PFS between those cases that had higher and lower PR expression, with a concurrent high ER expression, we observed that cases with a high PR expression (Allred score of 6–8) had a longer PFS (PFS 14 ± 8.1 Vs 10 ± 5.8 months respectively) than that seen in cases with lower PR expression (Allred score of ≤ 5). This observation is consistent with the idea that PR expression is generally associated with a better prognosis and higher response rates to endocrine therapies.[31] These results also agree with the current consensus that tumors with strong expression of ER/PR have a favorable risk profile.[32]

Studies have shown that higher Ki-67 levels are associated with reduced response to endocrine therapy and poorer prognosis.[7] The most commonly used cutoff for Ki-67 expression in clinical practice is ~14 and 20%.[7,33–35] We did not find any correlation between Ki-67 expression and parameters other than laterality and molecular type, possibly due to all patients presenting with an advanced stage of the disease.

Of note, endocrine resistance is the one that develops within 12 months of starting and while on first-line endocrine treatment in dMBC, while patients who have PFS of more than 12 months are supposedly endocrine sensitive.[20] Accordingly, our study showed 25 dMBC patients who had PFS of <12 months. However, out of these, only 14 patients received first-line hormonal therapy, implying that ~31.81% (14 out of 44 dMBC who progressed on HT) were endocrine resistant, similar to that observed in Caucasian population.[7,8]

Conclusion

In a nutshell, we found that the involvement of multiple organs was the strongest contributor in determining PFS. Patients with de novo metastatic presentation have better phenotypic characteristics such as lower histological grade, older age of presentation, and longer PFS compared with those who progressed to metastasis from earlier stage of the disease. ER, PR, and Ki-67 expression have limited value in predicting the treatment outcome in HR-positive HER2-negative MBC patients treated with endocrine therapy. We further suggest the exploration of additional immunohistochemical markers or molecular mechanisms that are affecting the ER signaling for a better understanding of endocrine resistance. Some of the limitations of this study are small sample size and retrospective design.

Note

This study was presented at the 3rd DALOS (Dr. Advani's Legendary Oncology Series) Conference, Mumbai, July 16, 2023.

Conflict of Interest

None declared.

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