Biological and Clinical Sciences Research Journal
eISSN: 2708-2261; pISSN: 2958-4728
www.bcsrj.com
DOI: https://doi.org/10.54112/bcsrj.v2023i1.370
*Biol. Clin. Sci. Res. J., Volume, **2023**: 370*
Original Research Article

CLINICAL FEATURES AND OUTCOMES OF PATIENTS WITH METASTATIC BREAST CANCER

RASHID AA[*1], TOOR MT[2], MUNIR AB[3]. ABRO NA[4], SHAFIQ B[5]

[1]*Department of Medical Oncology, Hameed Latif Hospital, Lahore, Pakistan*
[2]*Department of Orthopedics, Jinnah Hospital, Lahore, Pakistan*
[3]*Department of Medical Oncology, The University of Lahore Teaching Hospital, Lahore, Pakistan*
[4]*Department of Oncology, Jinnah Postgraduate Medical Centre (JPMC) Karachi, Pakistan*
[5]*Department of Oncology, Gujranwala Institute of Nuclear Medicine (GINUM), Pakistan*
**Correspondence author email address: drkhan1224@yahoo.com*

(Received, 27th January 2023, Revised 20th May 2023, Published 28th June 2023)

Abstract: *The retrospective study was conducted in the Department of Oncology, Hameed Latif Hospital, JPMC & GINUM, from January 2020 to January 2023 to assess the shift in the prognosis of MBC over time in the real-life clinical setting. Patients were divided into groups based on disease diagnosis (Group I: January 2020-January 2021 and Group II: January 2022-January 2023) and disease presentation (de novo vs. recurrent), and the correlation between prognostic factors and survival was assessed. A total of 781 patients were included in the study, 240 in Group I and 541 in Group II. There were 484 (61.9%) HR+, 210 (26.8%) HER2+, and 86 (11.01%) TN cases. 412 (53%) had recurrent disease, with a gradual increase in frequency (P <0.001). Incidence of HR+ disease (56%) was significantly higher than HER2+(20%) and TN subtypes (12%)(P<0.001). 375 (48%) had dnMBC, consisting of 52% with HR+ disease, 29% withHER2+ and 5.8% having TNMBC. Despite a gradual decrease in frequency, de novo disease was most common in the HER2+ subtype (62% in Group I vs. 49% in Group II, P = 0.007). A higher number of subjects with HR+ disease had chemotherapy in Group I compared to Group II (P=0.01), while endocrine therapy (ET) was more common in Group II (n = 238, 44%) compared to Group I (n = 118; 38.4%) (P=0.14). There were significant variations among pathological subtypes; HR+ was 18.0 months, HER2+ was 17.0 months, and TNBC was 10 months (P< 0.001). The median OS among all patients after a follow-up of 36 months was 50.0 (47.0-54.0) months. TN group had the worst OS of 27 months (P<0.001). The impact of modern treatment approaches in Group I vs. Group II (52 vs. 52 months) was insignificant. Advancement in the treatment is associated with improved prognosis of MBC, particularly for luminal B-HER2+. TNBC has the worst prognosis and is the most challenging to treat. The findings of this study will provide insight into disease patterns and survival, which can be valuable for improving outcomes through the use of novel treatment.*

Keywords: Metastatic Breast Cancer, Prognostic Factors, Chemotherapy, Immunotherapy, De Novo Breast Cancer, Recurrent Disease

Introduction

Pakistan has a high rate of breast cancer; even young women present at advanced stages with worse prognoses. There is an increasing prevalence of breast, uterine, cervical, and ovarian cancer among rural and urban women (Asghar et al., 2019). Though there has been an improvement in the prognosis of some types of metastatic breast cancer (MBC) over time, the outcome majorly depends upon disease presentation and genomic landscape, patient-related factors, and access to modern drugs and healthcare (Allemani et al., 2019; Lord et al., 2022). Increased awareness and modern diagnostic techniques, especially in segments with high income and good health infrastructure, are associated with decreased de novo metastatic occurrence. Its incidence rate has reduced from 25%- 28% at the beginning of the century to 6% -9% in the last ten years (Den Brok et al., 2017; Hood et al., 2023). This change in the metastatic pattern gradually impacted prognosis, as metastasis after the early stage is associated with a worse prognosis. The low survival rate of recurrent MBC is due to various adverse factors like presence of resistant clones or higher incidence of triple-negative BC (TNBC) (Hölzel et al., 2017; Malmgren et al., 2018). It is important to understand prognostic variance to better understand the impact of novel treatment methods for various pathological subgroups. Thus, the aim of this study is to assess shift in the prognosis of MBC over time in real life clinical setting.

[Citation: Rashid, A.A., Toor, M.T., Munir, A.B., Abro, N.A., Shafiq, B.. (2023). Clinical features and outcomes of patients with metastatic breast cancer. *Biol. Clin. Sci. Res. J.*, **2023***: 370*. doi: https://doi.org/10.54112/bcsrj.v2023i1.370]

Methodology

The retrospective study was conducted in the Department of Oncology, Hameed Latif Hospital, JPMC & GINUM, from January 2020 to January 2023. The Patients aged >18 years diagnosed with metastatic breast cancer were included in the study. Non-visceral disease is metastasis to soft tissue, skeletal or distant lymphatic. Pathological subtypes of recMBC were defined based on metastatic sites, as the biopsy shows. Hormone-responsive disease (HR+) was defined as the expression of membranous progesterone or estrogen receptor in 1% of tumor cells. Disease was classified as Luminal A if PR ≥20% (+), ER ≥10% (+), Ki 67 < 20% and Her2 (−), and Luminal B if Ki67 > 20% or PR < 20%. ASCO CAP guidelines were used for assessing human epidermal growth factor receptor 2 (HER2). Tumors not expressing HER2, PR, or ER were classified as TNBC.

Details about the patient's initial diagnosis with recMBC and treatment protocol were obtained from the medical record. First-line treatment refers to initial therapy given after disease diagnosis but before progression. The endpoint was described as i) progression-free survival (PFS), which is the time from metastatic diagnosis to progression/ death; ii) overall survival (OS) is the period between diagnosis and death and iii) disease-free interval (DFI)is the time between diagnosis and first recurrence.

Patients were divided into groups based on disease diagnosis (Group I: January 2020-January 2021 and Group II: January 2022-January 2023) and disease presentation (de novo vs. recurrent), and the correlation between prognostic factors and survival was assessed. The primary endpoint was the assessment of the impact of modern treatment strategies on different prognostic subtypes. Secondary outcomes were assessment of disease patterns and outcomes. Informed consent of the participants was taken. The ethical board of the hospital approved the study.

SPSS version 23.0 was used for data analysis. Treatment patterns of recMBC and dnMBC cohorts were compared. Fisher's exact test or Chi-square test was used to compare categorical variables. Mann-Whitney U-test was used for the comparison of continuous variables. The Kaplan–Meier analysis was used for survival outcomes. The Cox regression analysis estimated Hazard ratios (HRs) and 95% confidence intervals (CIs). P value ≤ 0.05 was considered statistically significant.

Results

A total of 781 patients were included in the study, 240 in Group I and 541 in Group II. The median age of the participants was 48 years. There were 484 (61.9%) HR+, 210 (26.8%) HER2+, and 86 (11.01%) TN cases. 25% study population was < 40 years. At presentation, significantly more cases had bone-only disease in HR+ compared HER2+ and TN subtypes (P<0.001) in both groups. Moreover, there were more patients < 40 years with MBC in Group II.

Of 781 patients, 412 (53%) had recurrent disease, with a gradual increase in frequency (48% in Group I vs.56% in Group II, P <0.001). More premenopausal patients were in the recMBC Group than the de novo Group (P<0.001). 359 (46%) patients had bone disease only, 343 (43.9%) had visceral involvement, and 78 (10%) had CNS metastasis. Incidence of HR+ disease (56%) was significantly higher than HER2+(20%) and TN subtypes (12%)(P<0.001). Time-dependent variation in the recMBC group showed a significant increase in HR+ patients in Group II (n = 330; 61%) vs. Group I (n = 117; 48.7%) (P = 0.004). There was an opposite trend for HER2+ (Group II: n = 97, 17.9% vs. Group I: n = 48, 20% P= 0.277) and TN patients (Group II: n = 54, 9.9% vs. Group I: n = 31, 12.9% P = 0.247).

Of 781 patients, 375 (48%) had dnMBC, consisting of 52% with HR+ disease, 29% withHER2+ and 5.8% having TNMBC. Despite the gradual decrease in frequency, de novo disease was most common in the HER2+ subtype (62% in Group I vs. 49% in Group II, P = 0.007). HR+ subgroup had a higher skeletal metastasis ratio than HER2+ and TN patients (P <0.001). TN patients had the highest ratio of CNS involvement compared to HR+ and HER2+ = subgroups (P = 0.313).

A significantly higher number of subjects with HR+ disease had chemotherapy (CT) in Group I (n=115, 47.9%) compared to Group II (n=210,38.8%) (P=0.01), while endocrine therapy (ET) was more common in Group II (n = 238, 44%) compared to Group I (n = 118; 38.4%) (P=0.14). A small number of patients in Group II received first-line treatment as ET + CDK inhibitors (n=32, 5.9%). In the HER2+ subgroup, 39% of patients in Group I and 35% in Group II received first-line CT + HER2 blockade. In Group II, 103 (19%) patients received CT + dual HER2 blockade along with pertuzumab and trastuzumab, more frequently in de novo than recurrent patients (P=0.06). More patients with TNBC in Group II (n=178, 32.9%) received platin-based CT compared to Group I (n=53,22%). 65 (12%) patients in Group II received immunotherapy +CT.

Median PFS at the initial treatment was 16.0 (15.0-17.0) months. There were significant variations among pathological subtypes; HR+ was 18.0 months, HER2+ was 17.0 months, and TNBC was 10 months (P< 0.001). The median OS among all patients after a follow-up of 36 months was 50.0 (47.0-54.0) months. TN group had the worst OS of 27 months (P<0.001). The impact of modern treatment approaches in Group I vs. Group II (52 vs. 52 months) was insignificant. However, time-related variations were observed in HR+ and HER2+ subgroups. There was a significant decrease in OS (P=0.01) and PFS (P=0.01) in dnMBC than recMBC. Analysis of DFI showed that the TNBC group had significantly higher overall survival in DFI < 24 months vs. DFI ≥ 24 (20 vs. 37 months, P=0.04). According to univariate analysis,

[Citation: Rashid, A.A., Toor, M.T., Munir, A.B., Abro, N.A., Shafiq, B.. (2023). Clinical features and outcomes of patients with metastatic breast cancer. *Biol. Clin. Sci. Res. J.*, **2023***: 370*. doi: https://doi.org/10.54112/bcsrj.v2023i1.370]

older age (≥50), 3 metastatic sites, recurrent disease, CNS and visceral metastatic involvement, luminal B and TNBC, and HER2+ subtypes were significantly associated with poor outcomes (Table I). Analysis of recurrent patients showed that older age, stage III at diagnosis, visceral metastasis, and luminal B were independent prognostic factors for poor OS (Table II).

For the visceral dnMBC, dual-HER2 blockade with pertuzumab and trastuzumab was more frequently administered in Group II compared to Group I (P<0.001), leading to improved outcomes. Survival analysis showed significant improvement in de novo Group through dual blockade (Group I vs. II, 3-year OS: 63% vs. 85%, P=.009), particularly in those with luminal B HER2+ disease (P=.013), age < 40 years (P=.009) and visceral metastates (P=0.03).

Patients with HR+ recMBC in Group II, who received first-line ET than Group I, showed similar PFS and OS, despite the higher incidence of unfavorable prognostic factors like luminal B disease and endocrine resistance (P=0.04). In Group II, patients with recurrent luminal B had a significantly worse prognosis than those with recurrent luminal A (P=0.012). A comparison of time-related groups showed that luminal A patients receiving first-line ET had significantly better OS than those receiving CT (P=0.008). There was no significant OS difference in luminal B patients treated with ET and CT(P=0.135). There was no difference in PFS in both luminal A and B subtypes with either treatment.

TN patients had the worst outcome. Recurrent patients in Group II had significantly lower PFS (P=0.230) and worse OS (P=0.005) compared to Group I, most likely because of unfavorable prognostic factors like increased CNS metastasis and a high incidence of progressors at the early stage of diagnosis. Survival over the period did not improve significantly in the de novo Group.

Table I Analysis of OS in the whole study population with MBC

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (<50 vs. ≥50)	1.26 (1.06–1.54)	0.002	1.26 (1.08–1.55)	0.005
Metastatic pattern (De novo vs. Recurrent)	1.18 (1.05–1.47)	0.012	1.15 (0.98–1.43)	0.100
Groups (Group II vs. Group I)	0.87 (0.74–1.14)	0.713		
Subtype				
Luminal B	1.21 (1.0–1.51)	0.006	1.28 (1.05–1.68)	0.012
Luminal B-HER2+	0.79 (0.89–1.14)	0.353	0.75 (0.76–1.08)	0.187
HER2+	1.50 (1.03–1.89)	0.023	1.45 (0.54–1.33)	0.123
TNBC	2.66 (1.95–2.73)	<0.001	2.06 (1.87–2.65)	<.001
No. of metastatic sites	1.24 (1.02–1.59)	0.022	1.27 (1.06–1.69)	0.012
CNS metastasis	1.57 (1.18–2.06)	0.001	1.97 (1.56–2.63)	<0.001
Visceral metastasis	1.34 (1.15–1.53)	<0.001	1.36 (1.18–1.41)	<0.001
Use of ablative treatment/surgery	0.85 (.76–1.25)	0.643		

Table II Analysis of OS in recurrent patients with MBC

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P value
Age (<50 vs. ≥50)	1.42 (1.17–1.73)	<0.001	1.47 (1.11–1.64)	0.005
Groups (Group II vs. Group I)	0.87 (0.89–1.29)	0.778		
Subtype				
Luminal B	1.27 (1.14–1.81)	0.026	1.29 (1.14–1.77)	0.025
Luminal B-HER2+	0.76 (0.69–1.34)	0.413	0.87 (0.55–1.34)	0.875
HER2+	1.66 (1.14–2.60)	0.011	1.51 (0.76–2.44)	0.076
TNBC	2.23 (1.53–2.88)	<0.001	2.18 (1.59–3.16)	<0.001
DFI	1.05 (0.86–1.28)	0.506		
No. of metastatic sites	1.22 (1.10–1.62)	0.055		
Stage at presentation (I + II vs. III)	1.26 (1.11–1.58)	0.005	1.51 (1.31–1.80)	<0.001
CNS metastasis	1.25 (0.88–1.75)	0.067		
Visceral metastasis	1.67 (1.31–1.88)	<0.001	1.54 (1.32–1.82)	<0.001
Use of ablative treatment/surgery	0.82 (.51–1.07)	0.127		

[Citation: Rashid, A.A., Toor, M.T., Munir, A.B., Abro, N.A., Shafiq, B.. (2023). Clinical features and outcomes of patients with metastatic breast cancer. *Biol. Clin. Sci. Res. J.*, **2023***: 370*. doi: https://doi.org/10.54112/bcsrj.v2023i1.370]

Discussion

This study showed significant variation in the presentation and treatment outcomes of various subtypes of metastatic breast cancer over time. In this study, most patients were recurrent, and their ratio increased over time. Moreover, the results showed a time-dependent increase in refractory patients with metastasis within 2 years of BC treatment, especially in TN and HR+ subgroups. In TN patients, there was a gradual increase in de novo recurrent patients (DFI <24 months), while there was no change in the ratio of the HR+ subtype. This poor biological outcome in refractory recurrent cases is in line with previous study findings (Heller et al., 2019). Moreover, the HER2+ subgroup had a higher incidence of de novo presentation, confirming previous findings(Muller et al., 2022).

Though both the time-related groups were not different in age, there were more patients < 40 years in TN and HER+ subgroups. Studies show a consistent increase in unfavorable outcomes of the advanced stage in patients aged between 25 to 39 years, with a higher incidence of HER2+ and TN (Cathcart-Rake et al., 2021). Nevertheless, this study shows that younger age is the independent predictor of favorable outcomes. The median survival of the study population over the entire study duration was 50 months. Though, OS in de novo breast cancer was significantly longer than the recurrent disease (P=0.013). Our findings are comparable to previous studies reporting that Median OS ranged between 24-38 months, widely varying among subtypes (Cathcart-Rake et al., 2021; Lindman et al., 2022). However, the findings of our study suggest that a better prognosis may be associated with factors like age, modern diagnostic techniques, biological response to treatment, and histology, as suggested in previous studies (Giaquinto et al., 2022).

Though there was no difference in outcomes and patient characteristics in time-related groups, the only major difference was in the survival of the HER2+ subgroup. It became significant in Group II de novo luminal B-HER2+ cases. Despite the unfavorable profile and CNS metastasis, HER2+ dnMBC had favorable outcomes due to higher access to pertuzumab and trastuzumab in the later years. These results are comparable to the previous studies, which showed significantly better outcomes in de novo than recurrent HER2+ MBC patients (Gobbini et al., 2018). A surprising finding of this study is a better prognosis of the luminal B-HER2+ subgroup compared to other subtypes. This is consistent with the result of previous studies (Chavez-MacGregor et al., 2017; Cobleigh et al., 2020). However, OS in recurrent luminal A subjects was significantly longer than luminal B cases in Group B; This can be due to the shift in the choice of first-line treatment for HR+ from CT in Group I to ET in Group II. Our study's initial preference for CT contradicts previous studies and recent guidelines that reported ET as the treatment of choice for HR+ patients (Cardoso et al., 2020; Karadurmus et al., 2023). The limitation of our study is the retrospective nature of data on family history, genomic factors, menopausal status, and comorbid conditions.

Conclusion

Advancement in the treatment is associated with improved prognosis of MBC, particularly for luminal B-HER2+. TNBC has the worst prognosis and is the most challenging to treat. The findings of this study will provide insight into disease patterns and survival, which can be valuable for improving outcomes through the use of novel treatment.

Conflict of interest

The authors declared absence of conflict of interest.

References

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., Bonaventure, A., Valkov, M., Johnson, C. J., and Estève, J. (2019). Global surveillance of trends in cancer survival 2000-14 (CONCORD-3).

Asghar, K., Loya, A., Rana, I. A., Tahseen, M., Ishaq, M., Farooq, A., Bakar, M. A., and Masood, I. (2019). Indoleamine 2, 3-dioxygenase expression and overall survival in patients diagnosed with breast cancer in Pakistan. *Cancer management and research*, 475-481.

Cardoso, F., Paluch-Shimon, S., Senkus, E., Curigliano, G., Aapro, M., André, F., Barrios, C., Bergh, J., Bhattacharyya, G., and Biganzoli, L. (2020). 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Annals of Oncology* **31**, 1623-1649.

Cathcart-Rake, E. J., Ruddy, K. J., Bleyer, A., and Johnson, R. H. (2021). Breast cancer in adolescent and young adult women under the age of 40 years. *JCO oncology practice* **17**, 305-313.

Chavez-MacGregor, M., Mittendorf, E. A., Clarke, C. A., Lichtensztajn, D. Y., Hunt, K. K., and Giordano, S. H. (2017). Incorporating tumor characteristics to the American Joint Committee on Cancer breast cancer staging system. *The oncologist* **22**, 1292-1300.

Cobleigh, M., Yardley, D. A., Brufsky, A. M., Rugo, H. S., Swain, S. M., Kaufman, P. A., Tripathy, D., Hurvitz, S. A., O'Shaughnessy, J., and Mason, G. (2020). Baseline

characteristics, treatment patterns, and outcomes in patients with HER2-positive metastatic breast cancer by hormone receptor status from SystHERs. *Clinical cancer research* **26**, 1105-1113.

Den Brok, W. D., Speers, C. H., Gondara, L., Baxter, E., Tyldesley, S. K., and Lohrisch, C. A. (2017). Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. *Breast cancer research and treatment* **161**, 549-556.

Giaquinto, A. N., Sung, H., Miller, K. D., Kramer, J. L., Newman, L. A., Minihan, A., Jemal, A., and Siegel, R. L. (2022). Breast cancer statistics, 2022. *CA: a cancer journal for clinicians* **72**, 524-541.

Gobbini, E., Ezzalfani, M., Dieras, V., Bachelot, T., Brain, E., Debled, M., Jacot, W., Mouret-Reynier, M. A., Goncalves, A., and Dalenc, F. (2018). Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *European journal of cancer* **96**, 17-24.

Heller, D. R., Chiu, A. S., Farrell, K., Killelea, B. K., and Lannin, D. R. (2019). Why has breast cancer screening failed to decrease the incidence of de novo stage IV disease? *Cancers* **11**, 500.

Hölzel, D., Eckel, R., Bauerfeind, I., Baier, B., Beck, T., Braun, M., Ettl, J., Hamann, U., Kiechle, M., and Mahner, S. (2017). Improved systemic treatment for early breast cancer improves cure rates, modifies metastatic pattern and shortens post-metastatic survival: 35-year results from the Munich Cancer Registry. *Journal of cancer research and clinical oncology* **143**, 1701-1712.

Hood, V., Bandini, L., Carter, T., Schatz, A., Sweetenham, J., Smedley, W., Morales, J. F., Nellis, R. V., Jones, R. A., and Zonakis, L. (2023). NCCN Policy Summit: Cancer Care in the Workplace: Building a 21st Century Workplace for Patients, Survivors, and Caretakers. *Journal of the National Comprehensive Cancer Network* **21**, 459-464.

Karadurmus, N., Sendur, M. A. N., Cil, T., Oksuzoglu, O. B. C., Arslan, C., Harputluoglu, H., Goksu, S. S., Ozturk, B., Cubukcu, E., and Demirci, U. (2023). Abstract P4-03-40: Patient and treatment characteristics in HR+/HER2-metastatic breast cancer in a real-life setting. *Cancer Research* **83**, P4-03-40-P4-03-40.

Lindman, H., Wiklund, F., and Andersen, K. K. (2022). Long-term treatment patterns and survival in metastatic breast cancer by intrinsic subtypes–an observational cohort study in Sweden. *BMC cancer* **22**, 1-12.

Lord, S. J., Bahlmann, K., O'Connell, D. L., Kiely, B. E., Daniels, B., Pearson, S.-A., Beith, J., Bulsara, M., and Houssami, N. (2022). De novo and recurrent metastatic breast cancer–A systematic review of population-level changes in survival since 1995. *EClinicalMedicine* **44**.

Malmgren, J. A., Mayer, M., Atwood, M. K., and Kaplan, H. G. (2018). Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990–2010. *Breast cancer research and treatment* **167**, 579-590.

Muller, K., Joms, J. M., and Tozbikian, G. (2022). What's new in breast pathology 2022: WHO 5th edition and biomarker updates. *Journal of pathology and translational medicine* **56**, 170-171.