

PROGNOSIS OF METASTATIC BREAST CANCER: DIFFERENCES BETWEEN PATIENTS WITH DE NOVO AND RECURRENT METASTATIC BREAST CANCER

RASHID AA^{*1}, SHAFIQ B², ISMAIL Z¹, SATTAR MW³

¹Department of Oncology, Hameed Latif Hospital Lahore, Pakistan

²Department of Oncology, Gujranwala Institute of Nuclear Medicine, Pakistan

³Department of Medical Oncology, Multan Medical and Dental College (MMDC) Multan, Pakistan

*Correspondence author email address: drkash226@yahoo.com

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Abstract: The retrospective study was conducted in the Department of Oncology from January 2021 to January 2022 to evaluate prognostic factors and the prognosis of the patients with recurrent metastatic breast cancer compared to those with de novo metastatic breast cancer. The study was conducted on a total of 400 patients. Patients were categorized into three groups: A) de novo metastatic cancer (MFI < 3 months), B) recurrent metastatic cancer (MFI ≤ 24 months), and C) recurrent metastatic cancer (MFI > 24 months). The mean follow-up period was 37.2 months, after which 148 (37%) survived. Mean survival in de novo cancer was 30.1 months, and in recurrent cancer was 22.1 months (P=0.14). Subjects with de novo cancer had significantly better survival than those with early metastatic recurrence (MFI < 24 months) (P<0.0001). However, the difference between the survival of de novo and late metastatic recurrence (MFI > 24 months) was not statistically significant (P < 0.73). The difference in the impact of prognostic factors among the three metastatic groups was statistically significant (P=0.98). Thus, MFI is a significant prognostic factor for metastatic breast cancer; short MFI indicates an unfavorable prognosis. However, in our study, de novo cancer did not have a very poor prognosis.

Keywords: De Novo Metastatic Breast Cancer, MFI, Recurrent Metastatic Breast Cancer

Introduction

About 20 to 30% of cases of breast cancer develop distant recurrence (Dörr and Gabryś, 2018). Distant recurrence is mostly incurable, and the survival of such patients ranges from 2-3 years (Cardoso et al., 2020). The treatment outcome in malignant breast cancer is based on various prognostic factors. Subtypes of biological cancers based on human epidermal growth factor receptor 2 (HER2) and hormone receptor (HR) have different outcomes in case of distant recurrence (Liu et al., 2020). Other prognostic factors are the number, size, and performance status of distant recurrence and the patient's age.

Moreover, metastasis-free interval (MFI) is a major prognostic factor determining survival. MFI < 24 months leads to a worse prognosis (Lopez-Tarruella et al., 2019). MFI is incorporated in validated and clinically relevant prognostic models of metastatic breast cancer (Wong et al., 2019). With prognostic grouping based on MFI, distant metastasis at the initial breast cancer diagnosis may be considered the specific prognostic group called *de novo* metastatic breast cancer. This subgroup is hypothesized to have

a poor prognosis due to early metastasis. At the same time, it is suggested that *de novo* cancer has a better prognosis due to its response to systemic therapy. A previous study showed that *de novo* cancer had a superior prognosis to recurrent metastatic cancer (McKenzie et al., 2020). In another study, *de novo* HER2 metastatic cancer had a better prognosis than recurrent HER2 metastatic cancer (Cheng et al., 2022). However, a study reported that the prognosis for *de novo* and recurrent HER2 cancer treated with trastuzumab-based therapy did not differ significantly (Wong et al., 2019). In this study, we will evaluate prognostic factors and the prognosis of the patients with recurrent metastatic breast cancer compared to those with *de novo* metastatic breast cancer.

Methodology

The retrospective study was conducted in the Department of Oncology from January 2021 to January 2022. The study included patients with metastatic breast cancer. Informed consent of the participants was taken. The ethical board of the hospital approved the study. Participants'

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demographic data, tumor characteristics, size and number of metastasis, treatment information (chemotherapy and radiotherapy, surgery), and survival time was collected from the hospital record. Metastatic sites were classified as bone, skin, lump nodes, visceral (lymphangitic, lung, pleural, liver, pericardial, peritoneal, and carcinomatosis), brain, and multiple metastatic sites. TNM classification of malignant tumors (Amin et al., 2017) was used for characterizing tumors. HER2 positivity was a 2+ or 3+ immunohistochemistry score with positive fluorescence hybridization results. MFI was defined as the interval between primary breast tumor diagnosis and distant metastasis diagnosis. Patients were categorized into three groups: A) *de novo* metastatic cancer (MFI < 3 months), B) recurrent metastatic cancer (MFI ≤24 months), and C) recurrent metastatic cancer (MFI >24 months). Prognostic factors like age at the time of diagnosis of metastatic cancer, initial site and number of metastasis, and HER2 and HR status were included in the model. Cox proportional hazard model assessed the effect of these factors in three MFI-based categories. P-value<0.05 was considered statistically significant.

Results

The study was conducted with a total of 400 patients. 80 (20%) had *de novo*, and 320 (80%) had recurrent metastatic cancer. Of 320 patients, 86 (26.8%) had MFI <24 months, and 234 (73.1%) had MFI >24 months. The mean age of the participants with *de novo* cancer was 61 years, and those with recurrent cancer were 65 years. HR-positive cancer was more frequent in Group C (83%) and Group A (80%) compared with Group B (53%) (P<.0001). There was no significant difference in HER 2 positive statuses in all three groups.

In patients with early metastatic recurrence, 32.5% had visceral and 9.3% had brain metastasis. In *de novo* metastatic cancer, 24% had visceral, and 0% had brain metastasis. In late metastatic recurrence, 27% had visceral and 2.1% had brain metastasis (Figure 1)

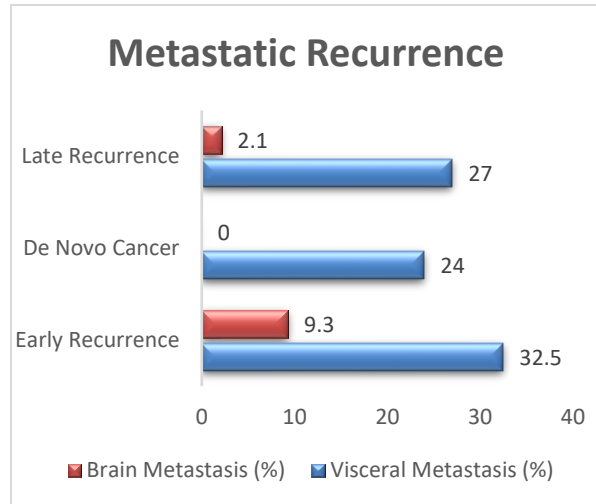


Figure 1 Metastatic Recurrence of breast cancer

The mean follow-up period was 37.2 months, after which 148 (37%) survived. Mean survival in *de novo* metastatic cancer was 30.1 months, while in recurrent metastatic cancer was 22.1 months (P=0.14). Subjects with *de novo* cancer had significantly better survival than those with early metastatic recurrence (MFI < 24 months) (P<0.0001). However, the difference between the survival of *de novo* and late metastatic recurrence (MFI > 24 months) was not statistically significant (P<0.73). The difference in prognostic factors' impact among the three metastatic groups was statistically significant (P=0.98). Table I summarizes a multivariate analysis of prognosis and prognostic factors in patients with metastatic breast cancer.

Table I Multivariable Analysis of Prognosis in metastatic breast cancer

Variables	Hazard Ratio	95% CI	P value
Early metastatic recurrence vs. <i>de novo</i>	1.96	1.48–2.61	<0.0001
Late metastatic recurrence vs. <i>de novo</i>	0.88	0.71–1.15	0.357
Age at the time of diagnosis	1.01	1.02–1.01	<0.0001
HR negative vs. positive	1.75	1.41–2.18	<0.0001
HER2 negative vs. positive	1.45	1.14–1.82	0.002
Initial visceral metastases vs. bone	1.81	1.31–2.21	<0.0001
Initial brain metastases vs. bone	2.32	1.41–3.82	0.001
Initial skin/lymph nodes metastases vs. bone	1.07	0.73–1.58	0.782
Multiple initial metastases vs. single metastases	2.31	1.82- 2.95	<0.0001

Discussion

In this study, we compared prognostic factors and survival of the patients with *de novo* metastatic breast

cancer and recurrent metastatic breast cancer. Both patients' prognoses were not statistically significant, irrespective of metastasis-free interval. The mean survival of participants with *de novo* cancer was 30.1

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months, comparable to previous studies (Guru et al., 2019). Patients with *de novo* metastatic breast cancer and late distant recurrence had similar outcomes, while those with *de novo* cancer had significantly better prognoses than those with early metastatic recurrence. Our study defined early recurrence as MFI <24 months, similar to previous studies (Ji et al., 2020; Lord et al., 2022).

Early metastatic recurrence is more likely associated with HR-negative breast cancer. Subtypes of breast cancer based on HER2 and HR have differences in metastatic recurrence; HR negative subgroup has an unfavorable prognosis and earlier recurrence compared to HR-positive subgroups (Gilbert et al., 2021). In the current study, survival between early distant recurrence and *de novo* cancer remained significantly different even after adjusting HR status. A better prognosis associated with *de novo* metastatic cancer may be explained by the management of early recurrent metastasis through adjuvant systemic therapy, which causes resistant metastasis compared to *de novo* metastatic cancer, which therapy is naive. However, in our study, survival of early distant recurrence and *de novo* cancer remained different even after excluding patients with recurrent metastasis who had adjuvant systemic therapy.

In this study, prognostic factors for survival were age at the time of diagnosis, initial site and number of metastasis, and HER2 and HR status. This is comparable to previous studies evaluating the prognosis of metastatic cancer (La Verde et al., 2021; Zimmerman et al., 2021). A previous study reported that HR-positive breast cancer had favorable outcomes compared to HR-negative breast cancer. HR positivity was a good prognostic and predictive factor in evaluating response to hormone therapy. The limitation of our study is the small sample size and retrospective study design. A larger study is recommended for further evaluation.

Conclusion

MFI is a significant prognostic factor for metastatic breast cancer; short MFI indicates an unfavorable prognosis. However, in our study, *de novo* metastatic cancer did not have a poor prognosis. *De novo* cancer showed better outcomes than late metastatic recurrence.

Conflict of interest

The authors declared an absence of conflict of interest.

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