ORIGINAL ARTICLE

Metastatic Trends in Breast Cancer According to Molecular Subtypes, Estrogen Receptor, Progesterone Receptor and Human Epidermal Growth Factor Receptor 2neu Status

Garima Uikey[1], Hemant Ahirwar[1], Rajesh Kori[1], Veenita Yogi[1], Suresh Yadav[1], Om Prakash Singh[1], Rishika Saxena[1], Sachet Saxena[1]

ABSTRACT

Background: Breast cancer molecular subtypes have been established a close relationship with site specific metastasis, disease prognosis, selection of therapy and response to therapy. This study is the evaluation of primary tumor molecular determinants and its clinical outcome in association with metastatic behavior of breast cancer. **Material and Methods**: This prospective study was included 221 patients of breast cancer registered in the department between January 2016 to December 2018. Based upon hormonal status, patients with breast cancer were categorized into four groups i.e. luminal (ER+,PR+, HER 2neu-), HER 2neu enriched (ER-, PR-, HER 2neu+), triple positive (ER+, PR+, HER 2neu+) and triple negative (ER-, PR-, HER 2neu-). Metastatic sites were divided into skeleton and visceral (lung, liver, and brain). The study data was compiled using Microsoft Excel sheet and Chi-Square test was used to assess the association between categorical variables. P value less than 0.05 was considered as statistically significant. **Results:** The mean age of the patients was 48.21±11.4 years (ranging from 22 to 80 years). About 36.7% and 24.9% patients were diagnosed as stage III A and stage II B respectively. Majority of patients were categorized as luminal (43%), followed by 24%, 17.2% and 15.8% as triple negative, triple positive and HER 2neu enriched respectively. Metastasis to bone following breast cancer was observed in majority i.e. 11.8% cases. Lung and liver metastasis observed in 6.3% cases each whereas brain metastasis was observed in 0.9% cases only. The higher proportions of TNBC cases metastasized to bone (22.6%), liver (7.5%), lung (7.5%) and brain (1.9%). The association between metastasis and hormonal status was statistically highly significant for bone metastasis ($p<0.05$). **Conclusion :** Breast cancer molecular subtypes have been related to considerable distinction in pattern of distant spread. Bone is the most predominant site of metastases followed by liver lung and brain. Luminal and HER 2 neu enriched subtypes having greater propensity for visceral metastasis where as TNBC predominantly show bone metastasis in this study.

KEY WORDS: Breast cancer, molecular subtypes, site-specific metastasis.

Introduction

Breast cancer is the most frequently diagnosed public health trouble and accounts for one-third of cancer cases in female throughout the world. According to the facts based totally on contemporary developments from the most cancers reviews through Indian Council of Medical Research (ICMR), breast cancer in female is the highest burden estimated to make a contribution 2,00,000 (14.8%) of the total cancer cases.[1,2] Metastasis ailment remains the underlying cause of loss of life in the majority of breast cancer patients who succumb to their sickness.[3] Breast cancer is a heterogenous disease that can be presented with varied clinical and pathological characteristics. Breast cancer has been considered to be developed from aberrations in genetic pathways resulted in uncontrolled cell growth with phenotypic changes such as ability to invade, neo capillarization

Access this article online

Quick Response Code:

Website: www.jmsh.ac.in

Doi: 10.46347/jmsh.v8i2.21.173

[1]Department of Radiation Oncology, Gandhi Medical College, Bhopal, 462001, Madhya Pradesh

Address for correspondence:

Veenita Yogi, Department of Radiation Oncology, Gandhi Medical College, Bhopal, 462001, Madhya Pradesh. E-mail: dryogi_vinita@yahoo.co.in

and metastasize. The genuine mechanism of metastasis development is nonetheless not well understood.[4]

The distant organs to which breast cancers most commonly metastasized are bone, liver, lung and brain. These sites are of scientific and organic importance and closely related to the patient's survival consequences.[2,5] Factors influencing development of breast cancer metastasis largely encompass tumor size, histology grade, lymphovascular spread, nodal involvement and receptors status.[6–8] Various published articles have been established a close relationship between molecular receptors status and prognosis, selection of therapy and response to therapy in breast cancer. The skeleton is amongst the most regularly located sites for approximately 50% of sufferers with breast cancer.[9]

It has been documented that patients with estrogen receptors (ER) positive and progesterone receptor (PR) positive tumors have greater probability for bone metastasis, whereas sufferers with human epidermal growth factor receptor 2neu (HER 2neu) enriched and ER-,PR-,HER2 neu-negative or triple-negative (TNBC) breast cancer have a predilection for visceral metastasis.[10,11] Present study is the evaluation of primary tumor molecular determinants and its clinical outcome in association with metastatic behavior of breast cancer.

Materials and Methods

This prospective observational study was conducted at the Government Medical College of Central India. This study was initiated and followed by approval from institutional ethical committee. The source of study was routine outpatients and inpatients breast cancer patients registered in the department between January 2016 to December 2018. A written informed consent has been obtained from each patient included in this study. The patient's statistics and pathological features of the primary tumor were recorded, including the patient's age at diagnosis, tumor type, histological grade and ER, PR and HER -2neu status. The detailed case history of the patient was recorded for the further investigations and the treatment as per required. Clinical prognosis and staging used to be carried out as per the necessities given in TNM staging, based on American Joint Committee on Cancer (AJCC) staging system.[12] Out of the 348 histopathologically proven cases of breast cancer, 221 patients included in the study. Patients with loco-regional recurrence or lymph node have been excluded.

The estrogen receptor (ER) and progesterone receptor (PR) expression repute used to be examined by means of immunohistochemistry (IHC). Nuclear staining in less than 1% cells were considered as negative, staining in 1-10% cells were focally positive and staining in more than 10% of tumor cells were considered as positive for ER and PR. Human epidermal growth factor receptor 2 neu (HER 2neu) expression was also examined by IHC, protein over expression and /or gene amplification used to be confirmed by Fluorescence in situ hybridization (FISH). Based upon hormonal status, patients with breast cancer were categorized into four groups i.e. luminal (ER+,PR+, HER 2neu-), HER 2neu enriched (ER-, PR-, HER 2neu+), triple positive (ER+, PR+, HER 2neu+) and triple negative (ER-, PR-, HER 2neu-).

Breast tumor spreading beyond the confines of the ipsilateral breast, chest wall, and regional lymph nodes defined as metastatic cancer. Metastatic sites were divided into skeleton and visceral (lung, liver, and brain).

Patients were totally scrutinized for the presence of metastases at the time of presentation. Pathological and laboratory investigations along with diagnostic work up, ultrasonography, chest X-ray, computed tomography scans were done routinely in every patient. Magnetic resonance imaging and positron emission tomography scans were done electively. Bone scintigraphy with technetium-99m was performed to assess bone metastasis on each patient.

Statistical analysis

The study data was compiled using Microsoft Excel sheet. The descriptive data analysis was done by SPSS software version 20, IBM, New York, USA. Chi-Square test was used to assess the association between categorical variables. The P value less than 0.05 was considered as statistically significant.

Results

This study was conducted on total of 221 patients of breast cancer with mean age of 48.21±11.4 years (ranging from 22 to 80 years). Majority of patients with breast cancer belonged to 31 to 60 years of age (84.15 %) whereas only five percent patients belonged to less than 30 years of age. Bilateral breast was involved in 0.9% cases. About 36.7% and 24.9% cancers were diagnosed as stage III A and stage II B

respectively (Table 1).

Table 1: Distribution according to baseline variables

Baseline variables		Number of patients	Percentage (%)
Age (in years)	21-30	11	5.0
	31-40	62	28.05
	41-50	62	28.05
	51-60	62	28.05
	>60	24	10.9
Breast site	Right	108	48.9
	Left	111	50.2
	Bilateral	2	0.9
TNM Stage of cancer	IIA	27	12.2
	IIB	55	24.9
	IIIA	81	36.7
	IIIB	35	15.8
	IIIC	17	7.7
	IV	6	2.7

Metastasis to bone following breast cancer was observed in majority i.e. 11.8% cases. Lung and liver metastasis observed in 6.3% cases each whereas brain metastasis was observed in 0.9% cases only (Figure 1).

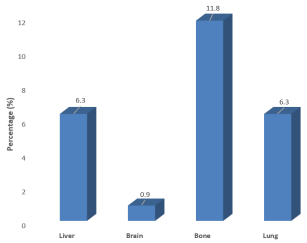

Figure 1: Distribution of metastasis according to sites

Based upon hormonal status, majority of patients were categorized as luminal (43%), followed by 24%, 17.2% and 15.8% cases as triple negative, triple positive and HER 2neu enriched respectively (Table 2).

This study revealed that higher proportions of triple negative breast cancer cases metastasized to bone (22.6%), liver (7.5%), lung (7.5%) and brain (1.9%) whereas metastasis was observed in only one case with triple positive cancer. The observed association between metastasis and hormonal status was statistically highly significant for bone metastasis ($p<0.05$), whereas no such association was observed for other metastasis ($p>0.05$) (Table 3).

Table 2: Distribution of patients according to hormonal status

Hormonal status	No. of patients	Percent
HER -2 enriched	35	15.8
Luminal	95	43.0
Triple negative	53	24.0
Triple positive	38	17.2

Table 3: Association between groups and distant metastasis

Distant metastasis	Hormonal status				P value
	HER-2 (n=35)	Luminal (n=95)	Triple negative (n=53)	Triple positive (n=38)	
Liver	1 (2.9)	9 (9.5)	4 (7.5)	0 (0)	0.172
Brain	1 (2.9)	0 (0)	1 (1.9)	0 (0)	3.27
Bone	4 (11.4)	9 (9.5)	12 (22.6)	1 (2.6)	0.023
Lung	2 (5.7)	8 (8.4)	4 (7.5)	0 (0)	0.33

The study data revealed that Triple negative cancer was associated with significantly higher proportions of metastasis to bone ($p<0.05$). However, no such association was observed for other hormonal status with metastasis ($p>0.05$) (Table 4).

Discussion

Breast cancer is a highly heterogenous disease which enclosed several subtypes with a variable, tendency to metastasize locally and to the distant organs, responses to treatment, and clinical outcomes. The mean age of presentation of breast cancer was early in this study as compared to a decade later worldwide.[13] The most common histological type of breast cancer was invasive (infiltrating) ductal carcinoma, composed 70%to 80% of cases. In this study 78% were ductal carcinoma and remaining were lobular, medullary, papillary and pleomorphic carcinoma.

The classification of breast cancer on the groundwork of molecular subtypes through DNA microarray gene expression analysis study by Perou et al, has validated prognostic and predictive significance. Molecular subtypes influencing most breast cancers management over the previous decade.[14] A prognostic factor provides information on clinical outcome at the time of diagnosis, or course of

Table 4: Association between groups and distant metastasis

Distant metastasis		Hormonal status							
		HER-2		Luminal		Triple negative		Triple positive	
		+	-	+	-	+	-	+	-
Liver	+	1 (2.9)	173(93)	9(9.5)	5 (4)	4(7.5)	10(6)	0(0)	14(7.7)
	-	34(97.1)	13 (7)	86(90.5)	121(96)	49(92.5)	158(94)	38(100)	169(92.3)
	P value	0.36		0.09		0.68		0.08	
Brain	+	1(2.9)	1(0.5)	0(0)	2 (1.6)	1(1.9)	1(0.6)	0(0)	2(1.1)
	-	34(97.1)	185(99.5)	95(100)	124(98.4)	52(98.1)	167(99.4)	38(100)	181(98.9)
	P value	0.18		0.22		0.39		0.52	
Bone	+	4(11.4)	22(11.8)	9(9.5)	17(13.5)	12(22.6)	14(8.3)	1(2.6)	25(13.7)
	-	31(88.6)	164(88.2)	86(90.5)	109(86.5)	41(77.4)	154(91.7)	37(97.4)	158(86.3)
	P value	0.95		0.36		0.005		0.06	
Lung	+	2(5.7)	12(6.5)	8(8.4)	6(4.8)	4(7.5)	10(6)	0(0)	14(7.7)
	-	33(94.3)	174(93.5)	87(91.6)	120(95.2)	49(92.5)	158(94)	38(100)	169(92.3)
	P value	0.87		0.27		0.68		0.08	

the metastatic disease, independent of undergoing therapy. By contrast, a predictive factor provides information on the possibility of response to a given therapy. The presence of HER2 neu over expression in breast cancer have both prognostic and predictive significance.[15] Estrogen receptor positive tumors demonstrates a more favorable outcome than the ER negative one.

The characterization of breast cancer metastasis to bone has been most notably studied for the reason that skeleton is the most common site of remote relapse.[16] Liede et al reported that patients with stage I to IIIbreast cancer will eventually develop bone metastases in up to 13.6% of all cases.[17] A study by Smid et al evident that bone relapse is most abundant in the luminal subtypes, whereas in the current study luminal subtypes comprised of 43%, which shows metastasis equally for liver and bone followed by lung. Hormone receptor–positive tumors are more likely to spread to bone as the initial site of metastasis.[18] In a SEER study by Wu et al patients with metastasis were distributed as respectively; 30-60% have lesion in the bone, 4—10% in the brain ,15-32% in the liver and 21-32% in the lung. Triple negative breast cancer (TNBC) has the greatest tendency to metastasize to the lung; occurring in 32% of patients compared to 21% of luminal A/B and 25% of HER2 neu positive patients.[19,20] In our study triple negative has tendency to metastasize to bone, liver ,lung, brain: 22.6%,7.5%,7.5% and 1.9% respectively. Brain metastases is infrequent as the first site of distant recurrence in the present series 2.9% and 1.9% in HER 2neu enriched and TNBC respectively , but an increasing rate of brain metastases is reported in recent years. An early observation exhibits a trend of affiliation with the HER 2neu enriched subtype and an inclination for fewer liver focused events in patients with the luminal subtype. Liver metastases in our study stipulate that 9.5% in luminal, 7.5 % and 2.9% in triple negative and HER 2neu enriched respectively. For the lung metastases in patients, it demonstrates that 8.4% in luminal, followed by 7.5% in TNBC and 5.7% in HER 2neu enriched.[21] A population-based study reported that both metastatic sites and molecular subtypes remarkably affected the overall survival after metastasis. The percentage of bone metastasis (59.9%) were higher in luminal subtypes followed by lung, liver and brain. HER 2neu enriched patients presented with higher percentage of liver metastasis. TNBC patients presented with increased proportion of visceral metastasis with higher proportion of brain metastases. This study concluded that luminal subtypes patients presented with bone metastasis luminal, and HER 2neu enriched and TNBC presented with visceral metastases.[22]

This study has some potential limitations due to short period, limited sample size and the lack of more comprehensive molecular profiling. We did not appraise the outcome of therapy on survival in the present study.

Conclusion

Breast cancer stays a huge burden in current society, requiring in addition search to apprehend the underlying mechanism that stress metastases and how to intention it. The understanding of molecular determinants and their association with prognosis, selection of therapy and response to therapy have led to the absolutely anatomic staging for breast cancer being contested. Subtypes had been related to considerable distinction in pattern of distant spread. Bone is the most predominant site of metastases followed by liver lung and brain. Luminal subtype having greater propensity for visceral metastasis where as TNBC predominantly show bone metastasis.

References

1. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Global Oncology. 2020;(6):1063–1075. Available from: https://doi.org/10.1200/GO.20.00122.
2. Chang J, Clark GM, Allred DC, Mohsin S, Chamness G, Elledge RM. Survival of patients with metastatic breast carcinoma: importance of prognostic markers of the primary tumor. Cancer. 2003;97(3):545–553. Available from: https://doi.org/10.1002/cncr.11083.
3. Redig AJ, Mcallister SS. Breast cancer as a systemic disease: a view of metastasis. Journal of Internal Medicine. 2013;274(2):113–126. Available from: https://doi.org/10.1111/joim.12084.
4. Pantel K, Woelfle U. Micrometastasis in breast cancer and other solid tumors. Journal of Biological Regulators and Homeostatic Agents. 2004;18(2):120–125.
5. Hess KR, Varadhachary GR, Taylor SH, Wei W, Raber MN, Lenzi R, et al. Metastatic patterns in adenocarcinoma. Cancer. 2006;106(7):1624–1633. Available from: https://doi.org/10.1002/cncr.21778.
6. Chia S, Norris B, Speers C, Cheang M, Gilks B, Gown AM, et al. Human Epidermal Growth Factor Receptor 2 Overexpression As a Prognostic Factor in a Large Tissue Microarray Series of Node-Negative Breast Cancers. Journal of Clinical Oncology. 2008;26(35):5697–5704. Available from: https://doi.org/10.1200/JCO.2007.15.8659.
7. Alanko A, Heinonen E, Scheinin T, Tolppanen EM, Vihko R. Significance of estrogen and progesterone receptors, disease-free interval, and site of first metastasis on survival of breast cancer patients. Cancer. 1985;56(7):1696–1700. Available from: https://doi.org/10.1002/1097-0142(19851001)56:7<1696::aid-cncr2820560738>3.0.co;2-n.
8. Soerjomataram I, Louwman MWJ, Ribot JG, Roukema JA, Coebergh JWW. An overview of prognostic factors for long-term survivors of breast cancer. Breast Cancer Research and Treatment. 2008;107(3):309–330. Available from: https://doi.org/10.1007/s10549-007-9781-7.
9. Kriege M, Seynaeve C, Meijers-Heijboer H, Collee JM, Menke-Pluymers MBE, Bartels CCM, et al. Distant disease-free interval, site of first relapse and post-relapse survival in BRCA1- and BRCA2-associated compared to sporadic breast cancer patients. Breast Cancer Research and Treatment. 2008;111(2):303–311. Available from: https://doi.org/10.1007/s10549-007-9781-7.
10. Niwinska A, Murawska M, Pogoda K. Breast cancer brain metastases: difference in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole- brain radiotherapy (WBRT). Annals of Oncology. 2010;21(5):942–948. Available from: https://doi.org/10.1093/annonc/mdp407.
11. Kennecke H, Yerushalmi R, Woods R, Cheang MCU, Voduc D, Speers CH, et al. Metastatic Behavior of Breast Cancer Subtypes. Journal of Clinical Oncology. 2010;28(20):3271–3277. Available from: https://doi.org/10.1200/JCO.2009.25.9820.
12. Amin MB, Edge S, Greene F, Compton C, Gernshenwald J, Brookland R. AJCC Cancer Staging Manual 8 th edition. New York. American Joint Commission on Cancer. 2017.
13. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast Cancer: Epidemiology and Etiology. Cell Biochemistry and Biophysics. 2015;72(2):333–338. Available from: https://doi.org/10.1007/s12013-014-0459-6.
14. Perou CM, Sørlie T, Eisen MB, Van De Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–752. Available from: https://doi.org/10.1038/35021093.
15. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study. JAMA. 2006;295(21):2492–2492. Available from: https://doi.org/10.1001/jama.295.21.2492.
16. Pareek A, Singh OP, Yogi V, Ghori HU, Tiwari V, Redhu P. Bone metastasis incidence and its correlation with hormonal and human epidermal growth factor receptor 2 neu receptors in breast cancer. Journal of Cancer Research and Therapeutics. 2019;15:971–976. Available from: https://doi.org/10.4103/jcrt.JCRT_235_18.
17. Liede A, Jerzak KJ, Hernandez RK, Wade SW, Sun P, Narod SA. The incidence of bone metastasis after early-stage breast cancer in Canada. Breast Cancer Research and Treatment. 2016;156(3):587–595. Available from: https://doi.org/10.1007/s10549-016-3782-3.
18. Smid M, Wang YX, Zhang Y, Sieuwerts AM, Yu J, Klijn JGM, et al. Subtypes of Breast Cancer Show Preferential Site of Relapse. Cancer Research. 2008;68(9):3108–3114. Available from: https://doi.org/10.1158/0008-5472.CAN-07-5644.

19. Lin Y, Yin W, Yan T, Zhou L, Di G, Wu J, et al. Site-specific relapse pattern of the triple negative tumors in Chinese breast cancer patients. BMC Cancer. 2009;9(1):342–342. Available from: https://doi.org/10.1186/1471-2407-9-342.
20. Wu Q, Li J, Zhu S, Wu J, Chen C, Liu Q, et al. Breast cancer subtypes predict the preferential site of distant metastases: a SEER based study. Oncotarget. 2017;8(17):27990–27996. Available from: https://doi.org/10.18632/oncotarget.15856.
21. Palmieri D, Smith QR, Lockman PR, Bronder J, Gril B, Chambers AF, et al. Brain Metastases of Breast Cancer. Breast Disease. 2007;26(1):139–147. Available from: https://doi.org/10.3233/bd-2007-26112.
22. Xiao W, Zheng S, Yang A, Zhang X, Zou Y, Tang H, et al. Breast cancer subtypes and the risk of distant metastasis at initial diagnosis: a population-based study. Cancer Management and Research. 2018;10:5329–5338. Available from: https://doi.org/10.2147/CMAR.S176763.

How to cite this article: Uikey G, Ahirwar H, Kori R, Yogi V, Yadav S, Singh OP, Saxena R, Saxena S. Metastatic Trends in Breast Cancer According to Molecular Subtypes, Estrogen Receptor, Progesterone Receptor and Human Epidermal Growth Factor Receptor 2neu Status. J Med Sci Health 2022; 8(2):100-105

Date of submission: 17.11.2021
Date of review: 20.11.2021
Date of acceptance: 10.03.2022
Date of publication: 27.08.2022