Imperial Journal of Interdisciplinary Research (IJIR)
Vol-3, Issue-8, 2017
ISSN: 2454-1362, http://www.onlinejournal.in

Pattern of Brain Metastasis in Immunohistochemistry Based Subtypes of Carcinoma Breast – An Institutional Study

Jyoti Poddar[1], Ashutosh Das Sharma[2], Sonal Patel Shah[3]
U Suryanarayan K[4]
[1]Assistant Professor, [2] MD Resident, [3]Associate Professor, [4]Professor
Department Of Radiotherapy, Gujarat Cancer and Research Institute
Ahmedabad, India.

Abstract: *The various subtypes of carcinoma breast show a distinct pattern of metastasis, which can aid in diagnosis and intervention, early in the course of the disease. Aim: To investigate the association between the Immunohistochemistry based subtypes of carcinoma breast and the incidence of brain metastasis in each subtype.Methods:400 patients of Carcinoma breast (stage II and III) were classified into luminal A/B, Her-2 enriched, luminal/Her-2 and Triple Negative subtypes based on the Estrogen receptor (ER), Progesterone receptor (PR), Her-2 status and Ki-67 levels. The pattern and incidence of brain metastasis in each molecular subtype was studied. Results: 143 patients developed metastasis and 38 of them had brain metastasis (26.5%). Brain metastasis was most common in Her-2 enriched subtype, 30.3% (n=20/38). But its incidence was comparatively lower in Luminal A/B subtype. The incidence of brain metastasis among all subtypes was found to be statistically insignificant (p value = 0.68) whereas the Pearson correlation was found to be 0.9197 which is a positive correlation. Conclusion:A correlation exists between the subtypes and the incidence of brain metastasis and Her-2 enriched subtype has the highest predilection. This knowledge can be used for greater vigilance for brain metastasis, and explore novel methods for its prophylaxis.*

1. Introduction

Although less common as compared to bone and liver metastasis in carcinoma breast, brain metastasis develop in about 30% of these patients [1]. Breast cancer is second only to lung cancer as a cause of brain metastases [2]. Brain metastasis carries the worst prognosis as it does not respond to systemic therapy like other visceral metastasis, and may lead to multiple neurological impairments and poor quality of life. There has been a recent rise in the incidence of brain metastases in patients of carcinoma breast, owing to improvement in diagnostic tools and the improved overall survival, provided by newer systemic therapies [3].

There are several risk factors which determine the possibility of brain metastasis in these patients such as, tumor size, grade of the tumour, younger age (<50 years), number of positive lymph nodes in the axilla(>4), shorter metastasis free survival (<24 months), genomic alterations etc [4].The grade of the tumour, lympho-vascular invasion, ER (estrogen receptor), PR (progesterone receptor) and Human epidermal growth factor receptor-2(Her-2) expression, are independent risk factors for recurrence and metastasis [5,6].

Patients with Her-2 positive breast cancer are two to four times more likely to develop CNS metastasis than patients with Her-2 negative disease. Triple negative and Her-2 positive patients have been reported to have an incidence of 20-30% and 25-35% of brain metastasis respectively with higher rates of first recurrence as brain metastases in triple negative [7]. The incidence is commoner in Her-2 enriched and luminal/Her variety.

In this study, we evaluated the ER, PR and Her-2 expression data of primary breast cancer patients by Immunohistochemistry (IHC) and the incidence of brain metastasis in each subtype. A better and beforehand understanding of pattern of brain metastasis may influence adjuvant therapy and surveillance strategies. The following analysis is presented: 5 year cumulative incidence of brain metastasis among patients of luminal A/luminal B, luminal/Her-2, Her-2 enriched, and triple negative subtypes.

2. Methods and materials

400 patients of Stage II and III (AJCC Staging system, 7th edition) Carcinoma breast without any evidence of Clinical or radiological distant metastasis at diagnosis were studied retrospectively from the period of January 2010- December 2011 and were

followed up till December 2015. Metastatic work up was been done for all the patients at the time of first presentation as per the institutional protocol which included chest X-ray for lungs metastasis, Ultrasound of abdomen and pelvis for liver metastasis, and bone scan (for stage III) for bone metastasis along with the routine investigation recommended for carcinoma breast. Patients' who had metastasis at the time of initial diagnosis, were excluded from the analysis.

All patients had undergone modified radical mastectomy as the primary treatment modality followed by adjuvant chemotherapy and radiotherapy. Adjuvant therapy was in the form of four cycles of Doxorubicin and Cyclophosphamide based chemotherapy followed by Postoperative radiotherapy (45 Gray in 20 fractions). The radiotherapy was followed by four cycles of taxane based chemotherapy followed by hormonal therapy for ER and PR receptor positive patients. None of the patients included in the study had received Trastuzumab.

The ER, PR and Her-2 status of all the patients were noted and the patients were accordingly classified into luminal A/B, HER-2 enriched, triple negative, and luminal/Her. Breast cancer subtypes were classified according to a gene expression profile validated IHC surrogate panel as follows: luminal A (ER positive and/or PR positive and Ki-67<=14%), luminal B (ER positive and/or PR positive and Ki-67 >14%), luminal/HER-2 (ER positive and/or PR positive and Her-2 positive), Her-2 enriched (ER negative, PR negative and Her-2 positive), Triple negative (ER negative, PR negative and Her-2 negative). Immunohistochemical (IHC) staining was performed for Estrogen receptor (ER), Progesterone receptor (PR), Her-2 and Ki-67 by fully automated machine VENTANA BENCHMARK XT. ER positivity and PR positivity were defined as any positive nuclear staining (>/= 1%) using Aldred scoring system, and Her-2 positive cases were defined by positive membranous scoring. For Her-2, IHC score of 3+ or IHC score of 2+ plus fluorescent in situ hybridization with amplification ratio >/= 2.0 was considered to be positive. The patients were followed up for development of brain metastasis which was categorized as brain parenchyma, pituitary gland, lepto-meningeal spread, choroid and frontal sinus. The incidence of brain metastasis was correlated with the molecular subtypes. MRI or CT scan of brain was used for diagnosis of brain metastasis. Table 1 shows the different subtypes classified in the study, and the distribution of each subtype in the study population respectively.

The *P* value was calculated and $P < 0.05$ was considered to be statistically significant. All calculations were done using SPSS 16.0 (Statistical Package for the Social Sciences version 16 produced by International Business Machines Corporation) software.

3. Results

Out of 400 patients studied, 104 were Luminal A/B type (26%), 148 were Her-2 enriched (37%), 84 were Luminal-Her type (21%) and 64 were triple negative type(16%). Out of 143 patients who developed metastasis, 38 patients had brain metastasis (26.5%) which is shown in Table 2. The incidence of brain metastasis was found to be statistically insignificant (p value = 0.68)

Table1 shows the different subtypes classified in this study

IHC based subtypes	ER receptor	PR receptor	Her-2 receptor	No. of patients
Luminal A/B	+	+	-	104
Her2 enriched	-	-	+	148
Luminal Her	+	+	+	84
Triple Negative	-	-	-	64

Table 2 shows the incidence of brain metastasis in various subtypes

Subtype	Brain metastasis (%)	Total percentage	P value
Luminal A/B	06/30(5.0)	26.5% (38/143)	0.68
Her-2 enriched	20/66(30.3)		
Luminal/Her	08/28(28.5)		
Triple negative	04/19(21.0)		

The patients who developed brain metastasis were classified into the IHC based subtypes. Out of 38 patients, 06 were luminal A/B (06/104), 20 were Her-2 enriched (20/148), 08 were Luminal/Her (08/84) and 04 were triple negative (04/64). The incidence was noted and a correlation was found between each subtype and the brain metastasis which is shown in Table 3. The Pearson correlation was found to be 0.9197 which is a positive correlation.

Table 3 shows the correlation between the molecular subtypes and brain metastasis

Subtype	Number (%)	Brain metastasis	Pearson Correlation

Luminal A/B	104 (26)	06	
Her2enriched	148(37)	20	0.919
Luminal/Her	84(21)	08	
Triple negative	64(16)	04	

Brain was most frequently metastasized in Her-2 enriched variety and Luminal/Her subtype.
Luminal A/B subtype develops brain metastasis less commonly.
Triple negative subtype has lesser incidence of brain metastasis but it is usually the first site of metastasis. All the four patients of triple negative variety had brain as the first site of metastasis.
None of the patients in any subtype developed brain metastasis as the sole site of metastasis. All the patients developed synchronous or metachronous metastasis in other sites, e.g. liver, bones lungs

4. Discussion

The incidence of brain metastasis in carcinoma breast has increasing, probably due to the following reasons:

1. Increase in detection rate due to usage of advanced imaging modalities like magnetic resonance imaging (MRI).
2. Improvement in survival of these patients, due to excellent control of disease, with advent of newer systemic therapies.
3. Low blood brain permeability of systemic agents.

Subtypes in breast carcinoma is proven to show a particular pattern of metastasis. Her-2, a member of the epidermal growth factor receptor tyrosine kinase family, is over expressed in 20-30% of human breast cancers [8]. Clinically, its over-expression is an independent adverse prognostic factor and is associated with an aggressive clinical course and poor survival in breast cancer patients[9]. Her-2 positive patients tend to develop brain metastasis in the course of the disease, more commonly than other subtypes. Park et al conducted a study of 313 carcinoma breast patients, and observed that the biological signature of the tumour, determines the chances of distant recurrence, and in turn, overall survival [10]. Brain metastasis was common in Her-2 enriched and Luminal/Her variety. Kallioniemi et al demonstrated that, Her-2 positive disease is associated with a different pattern of metastatic spread and those with over-expression of Her-2 gene metastasized three times more often ($p<0.0002$) to brain [11] Furthermore, Her-2 over-expression was shown to be a predictive factor for CNS metastases in advanced breast cancer [12]. Our study found a higher incidence of parenchymal CNS involvement in Her-2 positive patients in agreement with other studies [13,14,15].

Trastuzumab is proven to be beneficial in Her-2 positive patients in terms of improved local control and overall survival [16]. However, in few randomized trials, trastuzumab showed no effect on the incidence of isolated CNS metastases in patients of Her-2 positive disease. Trastuzumab has poor blood brain barrier (BBB) penetration, which could be a reason of this lesser efficacy. Although, it does not appear to prevent brain metastasis, in the absence of trastuzumab therapy, other visceral metastasis develop earlier, in the course of the disease, leading to organ failure which may cause the death of the patient, before development of brain metastasis. This hypothesis explains the reason of increase in incidence of brain metastasis in Her-2 positive patients on trastuzumab [17]. Lin et al conducted a study and concluded that patients of triple negative breast cancer, develop brain metastasis relatively earlier and their median survival after the development of metastasis was relatively less [18]. Malin et al reported that αB-crystallin is a novel regulator of brain metastasis in triple-negative breast cancer and represents a potential biomarker and drug target for this aggressive disease [19].

Current management of symptomatic and occult brain metastasis includes Whole brain radiotherapy (WBRT), Stereotactic Radiotherapy (SRS), and excision of a solitary mass. Hall et al reported that overall survival rate of patients with CNS metastases from breast cancer to be 8.0%, 6.9%, and 1.3% at 2 years, 3 years and 5 years respectively [20].The median survival for patients with breast cancer with untreated brain metastasis is one month which can be increased to 4‑6 months with whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS). It can be increased up to 16 months if solitary metastases can be removed surgically.

Early detection of brain metastasis is critical to enable intervention and minimize irreversible damage to the nervous system, which calls for certain preventive strategies that can ensure a delay in development of brain metastasis. Several hypotheses have been put forward for CNS prophylaxis for brain metastasis in these high risk group of patients like:

1. Frequent screening with imaging like MRI.
2. Use of alternative drugs in Her-2 positive disease which have better CNS penetration.
3. Prophylactic cranial irradiation (PCI).

Prophylactic cranial irradiation (PCI) has been proven to be a successful strategy in management of patients with Acute Lymphoblastic Leukaemia (ALL) and Small Cell Lung Cancer (SCLC) [21]. This strategy decreases the incidence of brain metastases and also prolongs survival [22].Therefore, this group of patients might benefit from prophylactic measures to prevent the occurrence of

CNS metastases as breast cancer resembles SCLC in many respects, namely systemic spread, predilection for brain metastasis, chemo-sensitivity etc. Huang et al [23] had conducted a prospective study where 24 patients of carcinoma breast were delivered prophylactic cranial irradiation (36Gray/20 fractions) which did not show any therapeutic benefit as patients developed brain metastasis even after PCI. There were caveats in the study like Stage III/IV patients were delivered PCI, after completion of chemotherapy. So this area needs to be explored further.

The way to effective CNS preventive strategy is identification of high risk patients based on imaging, clinical and pathological factors, subtyping and stringent follow up. A nomogram (designed and validated by M.D. Anderson Cancer Centre, USA) can be a very useful tool to predict the risk of brain metastasis [24]. A 13 gene signature study has been validated in Her-2 positive cancers, to predict the development of brain metastasis. In this study, the patients who belong to the "low risk signature" group had better brain metastasis free survival as compared to "high risk signature group" (77 months Vs 41 months; $P = 0.02$) , which was statistically significant [25]. Prospective study is warranted to provide evidence that screening for brain metastases prolongs overall survival and reduces symptoms.

5. Conclusion

From the results obtained in our study, we conclude that the different subtypes of carcinoma breast differ in tumor aggressiveness. The most common subtype was Her-2 enriched which comprised of 37% (n=148) of the study population. 44.5% of all Her-2 positive patients, developed metastasis and 30.3% of these was brain metastasis. Therefore, brain metastasis was predominantly seen in Her-2 enriched variety, which implies this subtype carries a poor prognosis, although, the site of distant relapse does not show any association with prognosis per se. Triple negative patients have first site of metastasis as brain.

Analysis of IHC based subtypes and different clinical and pathological parameters is important, as it can provide valuable information pertaining to prognosis. Patients, in whom brain metastasis can be anticipated, may be asked to participate in clinical trials involving novel drugs with high blood brain barrier permeability like Lapatinib. Prospective studies of Prophylactic cranial irradiation in this group of patients can be tried to evaluate its outcome. As the incidence of brain metastases from breast cancer appears to be rising, it is very important for clinicians to be aware of this disease process, its implications and potential treatment. Anticipation and management of brain metastases requires novel powerful imaging technologies, molecular targeted treatments, and multimodal, minimally invasive procedures.

10. References

[1] Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J ClinOncol 2004; 22:3608–3617.

[2] Wen PY, McLaren Black P, Loeffler JS. Treatment of metastatic cancer. In: DeVita VT, Hellman S, Rosenberg SA,editors. Cancer: Principles and Practice of Oncology. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 2655–2670.

[3]Frisk G, Svensson T, Backlund LM, Lidbrink E, Blomqvist P, Smedby KE. Incidence and time trends of brain metastases admissions among breast cancer patients in Sweden. Br J Cancer 2012;106:1850–1853.

[4] Tham YL, Sexton K, Kramer R, Hilsenbeck S, Elledge R. Primary breast cancer phenotypes associated with propensity for central nervous system metastases. Cancer. 2006;107:696–704.

[5]Alanko A, Heinonen E, Scheinin T. Significance of estrogen and progesterone receptors,disease-free interval, and site of first metastasis on survival of breast cancer patients. Cancer 1985;56:1696-1700

[6] The metastatic niche: Adapting the foreign soil Nat Rev Cancer 2009 Apr; 9(4): 285–293.

[7] Gori S, Rimondini S, De Angelis V, Colozza M, Bisagni G, Moretti G. Central nervous system metastases in HER-2 positive metastatic breast cancer patients treated with trastuzumab: Incidence, survival, and risk factors. Oncologist2007;12:766–773.

[8] Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: Correlation of relapse and survival with amplification of the HER2/neu oncogene. Science 1987;235(4785):177-182.

[9] Sjogren S, Inganas M, Lindgren A, Holmberg L, Bergh J. Prognostic and predictive value of c-erbB-2 overexpression in primary breast cancer, alone and in combination with other prognostic markers J Clin Oncol 1998;16(2):462-469.

[10] HyungSeok Park, Shinhyuk Kim, Kiho Kim, Ho Yoo World Journal of Surgical Oncology 2012, 10:4.

[11] Kallioniemi OP, Holli K, Visakorpi T, Koivula T, Helin HH, Isola JJ. Association of c-erb B 2 protein over-expression with high rate of cell proliferation, increased risk of visceral metastasis and poor long-term survival in breast cancer Int J Cancer 1991;49(5):650-655.

[12] Miller KD, Weathers T, Haney LG, Timmerman R, Dickler M, Shen J. Occult central nervous system involvement in patients with metastatic breast cancer Ann Oncol 2003;14(7):1072-1077.

[13] Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003;97(12):2972-2977.

[14] Clayton AJ, Danson S, Jolly S, Ryder WD, Burt PA, Stewart AL. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 2004;91(4):639-643.

[15]Shmueli E, Wigler N, Inbar M. Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment. Eur J Cancer 2004;40(3):379-382.

[16] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al: Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N EnglJ Med 2005;353:1659-1672.

[17] Gaedcke J, Traub F, Milde S, et al: Predominance of the basal type and HER-2/neu type in brain metastasis from breast cancer. Mod Pathol 2007;20:864-870

[18] Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases.Cancer 2008;113:2638–2645.

[19] Malin D, Strekalova E, Petrovic V. AlphaB-crystallin: a novel regulator of breast cancer metastasis to the brain. Clin Cancer Res 2014;20:56–67.

[20] Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17:279–286.

[21]Omura GA, Moffitt S, Vogler WR, Salter MM. Combination chemotherapy of adult acute lymphoblastic leukemia with randomized central nervous system prophylaxis. Blood1980;55(2):199-204.

[22] Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Eng J Med 1999;341:476-484.

[23]Huang F, Alrefae M, Langleben A, Roberge D Int J Radiat Oncol Biol Phys. 2009 ;73(3):752-758

[24]Graesslin O, Abdulkarim BS, Coutant C, Huguet F, Gabos Z, Hsu L, et al. Nomogram to predict subsequent brain metastasis in patients with metastatic breast cancer. J Clin Oncol. 2010;28:2032–2037

[25] Duchnowska R, Jassem J, Goswami CP, Dundar M, Gökmen-Polar Y, Li L. Predicting early brain metastases based on clinicopathological factors and gene expression analysis in advanced HER2-positive breast cancer patients. J Neurooncol 2015;122:205–216