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PROGNOSTIC FACTORS IMPLICATED IN THE DEVELOPMENT OF BRAIN METASTASIS FROM BREAST CANCER AND ITS INFLUENCE ON TIME:

Oncology

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ABSTRACT

Aim: To analyse the prognostic factors that could possibly contribute to the progression to brain metastasis in Ca Breast patients and to assess its influence on time to development.

Materials and Methods: A total of 22 carcinoma breast patients with brain metastasis who received Whole Brain Radiotherapy from January 2014 to September 2017 were retrospectively analysed. Median time to cerebral progression was analysed with respect to Stage of disease, Grade of tumour, Hormone Receptor and HER2 neu status, receipt of adjuvant chemotherapy and treatment with Trastuzumab in case of HER2 neu positive tumours. Statistical analysis was performed using Fisher Exact test.

Results: The median time to cerebral progression in patients with non-metastatic disease at presentation was 14 months (range 1-108 months). For Stage II disease, it was 27 months (range 1 – 108 months), for Stage III disease it was 9 months ($p = 0.1052$). The median time to cerebral progression was 22.5 months for those with Grade 2 tumours and 9 months (range 7 – 15 months) for those with Grade 3 tumours. ($p = 0.772$). In ER/PR+ tumours the median time to cerebral progression was 16 months whereas for those with ER/PR– tumours it was 13 months. ($p = 0.1191$) For the HER2 enriched subgroup, it was 8 months whereas for HER2– group the median time was 15 months. ($p = 0.4766$) Patients with triple negative tumours were noted to have a median time of 14 months. Among patients who received adjuvant chemotherapy their median time to cerebral progression was 14 months (range 3 – 108 months) compared to 12.5 months for those who did not receive adjuvant chemotherapy. ($p=0.08$) For patients with HER2+ positive tumours who received Immunotherapy with Trastuzumab, the median was 15 months compared to 8 months in those patients who did not receive Trastuzumab. ($p=1.000$). Additionally, in patients who had brain as the first metastatic site, the distribution of hormonal subtypes was as follows: ER+/HER2 - 1(9%), ER+/-HER2+ 5 (45%) and ER-/HER2- 5 (45%).

Conclusion: This study has enabled the identification of a subset of carcinoma breast patients who are at an increased risk for early development of brain metastasis. Those with Stage III disease, higher tumour grade, ER-, HER2 overexpressed tumours, those who did not receive adjuvant chemotherapy or those with HER2+ disease who did not receive Trastuzumab had a shorter time to development of brain metastasis.

KEYWORDS

Carcinoma breast, brain metastasis

Introduction:

Breast cancer is the second most common cause of brain metastasis after lung cancer. [1] Brain metastasis in breast cancer patients quite evidently indicates poor prognosis, with a median survival of 2–9 months despite treatment. [2–5] Subsets of patients with triple-negative or human epidermal growth factor receptor 2 (HER2)-positive tumours have been identified to have an increased risk for the development of brain metastasis. [6–9]

Management of brain metastasis poses a challenge as effective systemic therapy is underplay and current management options such as Surgical resection, Whole-Brain Radiotherapy (WBRT), Stereotactic Radiosurgery (SRS), cater to the achievement of optimum local control and delay neurological progression while chemotherapy, and targeted therapy may improve the overall outcome in these patients. [10,11]

The aim of this study is to analyse the prognostic factors that could possibly contribute to the development of brain metastasis in Ca Breast patients and to assess its influence on time to development. This could enable a better identification of high risk patients who would need to be additionally screened or who might require a more aggressive approach in management.

Materials and Methods:

A total of 22 carcinoma breast patients with brain metastasis who received Whole Brain Radiotherapy from January 2014 to September 2017 were retrospectively analysed. All patient included in this study received Whole Brain radiotherapy to a total dose of 30 Gy in 10 fractions delivered over two weeks using a 6 MV linear accelerator (LINAC) by lateral opposed fields.

Endocrine receptor status, ER, PR and HER2 neu was routinely assessed in all patients by Immunohistochemistry at the time of diagnosis. Tumours were classified as HER2/neu positive if they had a staining intensity of +++ whereas if a score of ++ was obtained, the tumours were re-analysed using FISH and tumours with HER2 neu gene amplification were deemed HER2 neu positive.

Median time to cerebral progression (time from diagnosis of primary till detection of brain metastases) was estimated and was analysed with respect to Stage of disease, Grade of tumour, Hormone Receptor and HER2 neu status, receipt of adjuvant chemotherapy and treatment with Trastuzumab in case of HER2 neu positive tumours. Statistical analysis was performed using Fisher Exact test. Patients with upfront Stage IV metastatic disease was not included in the analysis of time to progression.

Results:

Patient Characteristics:

All patients were suffering from histologically proven metastatic breast cancer. The median age at diagnosis of malignancy was 47 years. At diagnosis of primary disease, none of the patients had Stage I disease, 7 patients had Stage II disease, 7 patients had Stage III disease and 8 patients had primary metastatic Stage IV disease. 2 patients had Grade 2 tumour and 6 patients had Grade 3 tumour. In 14 patients the tumour grade was not available. At the time of detection of brain metastasis, 2 patients had metastasis to bone, 3 patients had metastasis to bone and viscera, 8 patients had metastasis to viscera only and the remaining 9 patients had no other extracranial metastasis, out of which 2 had presented with upfront brain metastasis. The distribution of hormonal subtypes of breast cancer was as follows: ER+/HER2- 4 (18%), ER+/HER2+ 3 (14%), ER-/HER2+ 6 (27%) and ER-/HER2- 9 (41%). In patients who developed metastasis to the brain as the first metastatic site, the distribution of hormonal subtypes was as follows: ER+/HER2- 1(9%), ER+/-HER2+ 5 (45%) and ER-/HER2- 5 (45%). See details in Table 1.

Table 1: Patient Characteristics

Characteristics	Patients
Median age at diagnosis	47 years
Stage at diagnosis	
Stage I	0
Stage II	7
Stage III	7
Stage IV	8
Tumour Grade	
Grade II	2
Grade III	6
Not known	14
Extracranial Metastasis	
Bone only	2
Bone + Viscera	3
Viscera only	8
Brain only Metastasis	9
Receptor Status (entire study group)	
ER+ HER2-	4 (18%)
ER+ HER2+	3 (14%)
ER- HER2+	6 (27%)
ER- HER2-	9 (41%)
Brain as first metastatic site	
ER+ HER2-	1 (9%)
ER+/- HER2+	5 (45%)
ER- HER2-	5 (45%)

Systemic Treatment:

Out of the patients who did not present with upfront metastasis, 2 received neoadjuvant chemotherapy and 12 received adjuvant chemotherapy. A total of 7 patients received endocrine therapy. 10 patients received palliative chemotherapy before the detection of brain metastasis whereas 4 patients received it after the detection of brain metastasis. Among the patients with Her2 positive status, 4 received systemic therapy with Trastuzumab whereas 5 patients did not receive Trastuzumab therapy. See details in Table 2.

Table 2: Systemic Treatment

Systemic Treatment	Patients
Neoadjuvant chemotherapy	2
Adjuvant chemotherapy	
Anthracycline based	1
Anthracycline + Taxane	10
Others	1
Endocrine Therapy	
Tamoxifen	3
Letrozole	4
Palliative Chemotherapy	
Anthracycline based	2
Taxane based	3
Anthracycline + Taxane	3
Others	4
More than one line of treatment	2
Trastuzumab	4

Time to Development of Brain Metastasis:

The median time to cerebral progression in patients with non-metastatic disease at presentation was 14 months (range 1-108 months). For Stage II and Stage III disease, median time was 27 months (range 1 – 108 months) and 9 months (p = 0.1052) respectively whereas the median time to cerebral progression in patients with upfront Stage IV extracranial metastatic disease was 8 months (range 5 – 8 months).

With respect to the Grade of the tumour, the median time to cerebral progression was 22.5 months for those with Grade 2 tumours and 9 months (range 7 – 15 months) for those with Grade 3 tumours. (p = 0.772)

On analysing the hormonal subtypes, it was noted that median time to cerebral progression for those patients with ER/PR + tumours was 16 months whereas for those with ER/PR – tumours it was 13 months. (p = 0.1191) For the HER2 enriched subgroup, the median time was 8 months whereas for HER2 – group the median time was 15 months. (p = 0.4766) Patients with triple negative tumours were exclusively analysed and it was noted that the median time to progression to brain metastasis was 14 months.

Among patients who received adjuvant chemotherapy their median time to cerebral progression was 14 months (range 3 – 108 months) compared to a median time of 12 months for those who did not receive adjuvant chemotherapy. (p=0.08) For patients with HER2+ positive tumours who received Immunotherapy with Trastuzumab, the median time to cerebral progression was 15 months compared to a median time of 8 months in those patients who did not receive Trastuzumab. (p=1.000)

All but one patient with upfront extracranial metastasis received Systemic Palliative therapy and their median time to cerebral progression was 8 months (range 5 – 8 months). See details in Table 3.

Table 3: Time to Brain Metastasis

Factors	Median Time	p value
Stage of Disease		
Stage II	27 months	0.1052
Stage III	9 months	
Grade of Tumour		
Grade 2	22 months	0.0772
Grade 3	9 months	
Hormonal receptor status		
ER/PR +	16 months	0.1191
ER/PR -	13 months	
Her2 neu status		
Her2 neu +	8 months	0.4766
Her2 neu -	15 months	
Triple Negative	14 months	
Adjuvant Chemotherapy		
Yes	14 months	0.08
No	12 months	
Trastuzumab Therapy		
Yes	15 months	1
No	8 months	

Discussion:

Brain metastasis remains one of the most catastrophic events of disease progression in carcinoma breast patients that is associated with the worst survival and quality of life. [12] Many studies in the past have explored the possible high-risk features in carcinoma breast patients that could lead to the development of brain metastasis and have attributed the same to negative hormone receptor status, Her2 neu overexpression, high tumour grading as well as presence of visceral metastasis, these factors typically indicate a more aggressive tumour phenotype. [13,14]

A study by Andre et al, showed that 38% of ER negative women developed brain metastases, compared to 14% of ER positive women. In our study, 32% of patients had ER+ disease whereas 68% had ER- disease. [15] Similarly, studies have noted that 40% of patients with HER2 neu + disease have a propensity for brain metastasis within two years compared to only 20% for the HER2 neu negative subset. [16,17] In our study, 41% had HER2 neu + disease and 59% had HER2 neu – disease.

In our study, we have analysed the time to the development of brain metastasis as this could help to identify a subgroup of patients with a markedly higher risk to early development of brain metastasis. The factors analysed were tumour grade, stage of disease, hormonal receptor and HER2 neu status, receipt of adjuvant chemotherapy and in HER2 neu + disease, the receipt of Trastuzumab. In a study by Fromm et all [(1)], higher tumour grade was associated with an early development of brain metastasis. In our study, although none of the factors showed a statistical significance with the time to development of brain metastasis, Stage III disease, higher tumour grade, ER-, HER2 overexpressed tumours, those who did not receive adjuvant chemotherapy and those with HER2 + disease who did not receive Trastuzumab had a shorter time to development of brain metastasis. Our analysis also showed that among patients with brain as the first site of metastasis 45% were HER2+ and triple negative tumours.

Although this study is a retrospective one on a small sample size which could pose as an indefinite limitation, it is of particular value as it helps to identify the high-risk groups that probably require screening or more aggressive treatment approaches. This could mandate the introduction of radiological methods of screening as it allows appropriate treatment of these patients at its asymptomatic stage before the onset of irreversible neurological damage.

Conclusion:

This study has enabled an identification of a subset of carcinoma breast patients who are at an increased risk for early development of brain metastasis. Those with Stage III disease, higher tumour grade, ER-, HER2 overexpressed tumours, those who did not receive adjuvant chemotherapy and those with HER2+ disease who did not receive Trastuzumab had a shorter time to development of brain metastasis.

Further studies on larger sample sizes maybe required to mandate a valid opinion.

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