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# Breast cancer subtypes and outcomes of central nervous system metastases

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ABSTRACT

Central nervous system (CNS) metastases are detected in up to one third of patients with advanced breast cancer, but their incidence and outcomes by breast cancer subtypes are not precisely documented. Herein, we retrospectively analyzed clinicopathologic data of 259 breast cancer patients with CNS metastases to evaluate the association between breast cancer subtypes and CNS metastasis. The patient groups were classified according to their hormone receptor status and HER-2 expression. Median follow-up time among the patients was 42 months and median survival after CNS metastasis detection was 7.8 months. In HER-2 overexpressing group, median time period between the diagnosis of breast cancer and the detection of CNS metastasis (15.9 months) was significantly shorter compared to the other groups ($p = 0.01$). The triple negative group had the shortest median survival time after CNS metastasis (6.6 months), although statistically not significant ($p = 0.3$). In multivariate Cox regression analyses, having solitary CNS metastasis (HR 0.4, 95% CI; 0.2–0.7, $p = 0.004$), and receiving chemotherapy after CNS metastasis (HR 0.4, 95% CI; 0.287–0.772, $p = 0.003$) were independent prognostic factors for increasing survival after CNS metastasis. In conclusion, new and effective treatment strategies are required for breast carcinoma patients with brain metastasis considering the positive effect of the treatment on survival.

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## Introduction

Breast cancer is one of the most common causes of central nervous system (CNS) metastases.[1] In early stage breast cancer, 10 year-incidence of CNS involvement is 5.2%[2]; whereas 10–15% of metastatic breast cancer (MBC) patients have CNS metastases.[3] However, the real incidence of CNS metastases with MBC patients is probably higher considering previously reported autopsy series with an approximately 30% proportion.[4,5]

CNS metastasis occurs later in the course of the metastatic disease, strongly affects the survival, and causes poor prognosis despite local and systemic chemotherapeutics. The median survival after CNS metastasis in breast cancer patients is approximately 4 months, and 1-year survival rate is 20%.[5–7] The discovery of distinct breast cancer subtypes each with unique clinicopathologic characteristics, and development of subtype-specific treatment modalities emerged the conduction of further studies analyzing the outcomes of different breast cancer subtypes.

The relapse pattern, survival and chemotherapy response are quite different between breast cancer subtypes.[8] Also, subtype-specific predilection to metastatic sites has been determined with gene-expression analyses.[9] While hormone receptor positive tumors tend to recur in bone, triple negative and HER-2 negative tumors are more likely to recur in viscera, including CNS.[10] High incidence and aggressive clinical behavior of CNS metastases have been suggested in triple negative breast cancer subtype by several studies with Eastern European and Asian patient populations.[11–14]

In the current study, survival outcomes of different breast cancer subtypes in MBC patients with CNS involvement were analyzed to evaluate their association considering the clinical characteristics of the patients.

## Material and methods

Clinical records of 259 breast cancer patients with CNS metastasis followed at the Ankara Oncology Research and Training Hospital, and Hacettepe University Institute of Oncology between January 1995 and March 2010 were analyzed retrospectively. Diagnosis of breast cancer was confirmed histologically. CNS metastases were determined by either contrast-enhanced

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**Table 1**
Factors affecting the time period between diagnosis of breast cancer and development of CNS metastasis, and median survival time after CNS metastasis.

| | *n* (%) | Median time for development of CNS metastasis (months)* | *p* | Median survival time after CNS metastasis (months)** | *p* |
|---|---|---|---|---|---|
| Total | 259 (100) | 31.4 | – | 7.8 | – |
| Histology of primary tumor | | | | | |
| IDC | 231 (91.7) | 31.4 | 0.48 | 8.1 | <0.001 |
| ILC | 12 (4.8) | 24.8 | | 3.0 | |
| Others | 9 (3.6) | 25.4 | | 2.9 | |
| Estrogen Receptor | | | | | |
| Positive | 98 (46.7) | 36.7 | 0.12 | 9.0 | 0.35 |
| Negative | 112 (53.3) | 25.4 | | 8.1 | |
| Unknown | | | | | |
| Progesterone Receptor | | | | | |
| Positive | 90 (45.0) | 33.8 | 0.33 | 10.2 | 0.38 |
| Negative | 110 (55.0) | 20.6 | | 8.2 | |
| HER-2 | | | | | |
| Positive | 105 (59.0) | 29.0 | 0.43 | 9.0 | 0.43 |
| Negative | 73 (41.0) | 28.2 | | 6.6 | |
| Breast Cancer Subtypes | | | | | |
| Luminal A | 48 (27.9) | 22.7 | 0.01 | 7.4 | 0.30 |
| Luminal B | 53 (30.8) | 40.4 | | 10.9 | |
| Triple negative | 21 (12.2) | 28.2 | | 6.6 | |
| HER-2 overexpressing | 50 (29.1) | 15.9 | | 8.2 | |
| Grade | | | | | |
| I | 13 (8) | 48.3 | 0.002 | 6.6 | 0.081 |
| II | 66 (40.5) | 36.9 | | 9.0 | |
| III | 84 (51.5) | 23.0 | | | |
| Stage at diagnosis | | | | | |
| I | 51 (20.8) | 42.6 | <0.001 | 5.1 | 0.7 |
| II | 109 (44.5) | 30.4 | | 11.5 | |
| III | 63 (25.7) | 28.3 | | 9.8 | |
| IV | 22 (9.0) | 10.2 | | | |
| Adjuvant Chemotherapy | | | | | |
| Yes | 201 (86.3) | 36.5 | 0.48 | | 0.66 |
| No | 32 (13.7) | 15.9 | | | |
| Adjuvant Radiotherapy | | | | | |
| Yes | 146 (64.9) | 37.6 | 0.31 | 7.5 | 0.43 |
| No | 79 (35.1) | 20.4 | | 7.5 | |
| Adjuvant Hormonotherapy | | | | | |
| Yes | 106 (46.7) | 39.6 | 0.003 | 7.4 | 0.96 |
| No | 121 (53.3) | 24.0 | | 7.5 | |
| Menopausal Status | | | | | |
| Premenopausal | 169 (66.2) | 38.5 | 0.007 | 7.8 | 0.60 |
| Postmenopausal | 80 (33.8) | 22.7 | | 7.4 | |
| Age at diagnosis of breast carcinoma | | | | | |
| ≤43[a] | 130 (50.2) | 36.7 | 0.14 | 11.9 | 0.86 |
| >44 | 129 (49.8) | 27.0 | | 8.1 | |
| Trastuzumab before CNS metastases (within the HER-2 positive patients) | | | | | |
| Yes | 55 | 22.0 | 0.67 | 12.0 | 0.45 |
| No | 48 | 26.1 | | 7.0 | |
| Trastuzumab after CNS metastases (within the HER-2 positive patients) | | | | | |
| Yes | 20 | 22.0 | 0.14 | 15.9 | 0.04 |
| No | 83 | 30.6 | | 7.5 | |

[a] Median age for breast cancer diagnosis.

computerized tomography or magnetic resonance imaging. The presence of estrogen and progesterone receptors (ER and PR) was detected by immunohistochemical (IHC) staining. HER-2 expression of primary and/or metastatic site was analyzed by IHC staining, and scored as 0, 1+, 2+, and 3+ according to strength of the staining. Fluorescent *in situ* hybridization (FISH) or silver *in situ* hybridization (SISH) was performed to 2+ tumors by IHC. HER-2 overexpression was defined as either 3+ by IHC or 2+ by IHC and positive for one of the ISH methods.

Four different breast cancer subtypes were determined according to hormone receptor status and HER-2 expression: ER and/or PR positive and HER-2 negative (luminal A), ER and/or PR positive and HER-2 positive (luminal B), ER and PR negative and HER-2 positive (HER-2 overexpressing) and triple negative. One hundred and seventy-two of the patients had receptor data for subtype classification.

Different clinical characteristics of the patients including age, premenopausal status, and stage at breast cancer diagnosis,

histological tumor characteristics, time interval between the diagnosis and first recurrence, site of first recurrence, number of metastases, type of CNS metastases (leptomeningeal (LM) or parenchymal), nature of CNS metastases (solitary or multiple), treatment modalities for breast cancer (adjuvant, and palliative), treatment modalities for CNS metastases (surgery, radiotherapy) and chemotherapy after CNS metastases, follow-up interval, and time period between the diagnosis and death were analyzed.

Statistical analyses were performed by using SPSS version 15.0 (SPSS Inc., Chicago, IL). A two-tailed $p < 0.05$ was considered statistically significant. Survival rates were calculated by Kaplan–Meier method, and different characteristics between groups were assessed by using log-rank test. Independent variables predicting survival were evaluated with Cox proportional hazards model, sharing in all variables with p values <0.20 in the univariate analysis. The 95% confidence interval was calculated for all hazard ratios (HRs) in Cox regression analysis.

## Results

### *Characteristics of patient population*

A total of 259 breast cancer patients with CNS metastasis were analyzed (Table 1). The median age was 43 (range 22–78) and 66.2% ($n = 169$) patients were premenopausal at the time of diagnosis of primary breast carcinoma. Most of the patients had invasive ductal carcinoma (IDC) ($n = 231$; 91.7%) and 51.5% ($n = 84$) of the patients had Grade III tumors. Of note, the tumor grades of 96 patients were not recorded. 63 patients (25.7%) had locally advanced disease and 22 (9.0%) had metastatic disease at the time of diagnosis. The percentages of the four different subtypes were 27.9% ($n = 48$) for Luminal A, 30.8% ($n = 53$) for Luminal B, 29.1% ($n = 50$) for HER-2 overexpressing, and 12.2% patients ($n = 21$) for triple negative subtype. 86.3% ($n = 201$) of the patients received adjuvant chemotherapy, whereas 64.9% ($n = 146$) received adjuvant radiotherapy. 55% of the patients with hormone receptor positive tumors had received adjuvant hormonotherapy. 52.3% ($n = 55$) of the HER-2 positive MBC patients were treated with trastuzumab plus chemotherapy for distant or locoregional recurrence before the detection of CNS metastasis.

Median overall survival (between the time of diagnosis and death or last contact) was 49.4 months. The CNS was found as the first metastatic site in 32 patients (14.1%). 53 (22.4%) patients had solitary CNS metastasis, and remaining 184 (77.6%) patients had multiple parenchymal metastases.22 patients (8.8%) had only LM and 229 (%91.2) patients had parenchymal metastasis (Table 2).

### *Time interval between the diagnosis of breast cancer and detection of brain metastasis*

The median age of 259 patients at the time of diagnosis of CNS metastasis was 47 years (range; 24–78). While median time period from the diagnosis of breast cancer to development of CNS metastases was 31 months (range; 0–180) totally, it was 22.7 months for luminal A; 40.4 months for luminal B; 15.9 months for HER-2 overexpressing, and 28.2 months for triple negative subtype ($p = 0.01$, Fig. 1). This time interval was significantly shorter in patients with high grade, advanced stage, and postmenopausal status at the time of diagnosis; and in the patients who did not receive adjuvant hormonotherapy (Table 1).

In multivariate Cox regression analyses, being in the HER-2 overexpressing group (HR 2.0 95% CI; 1,2–3,2; $p = 0.004$) and postmenopausal status (HR 1.6 95% CI; 1.0–2.5; $p = 0.044$) were only significant factors associated with the time period between diagnosis of breast cancer and detection of CNS metastasis.

**Table 2**
Association between overall survival after CNS metastases, and CNS metastasis characteristics with treatment modalities.

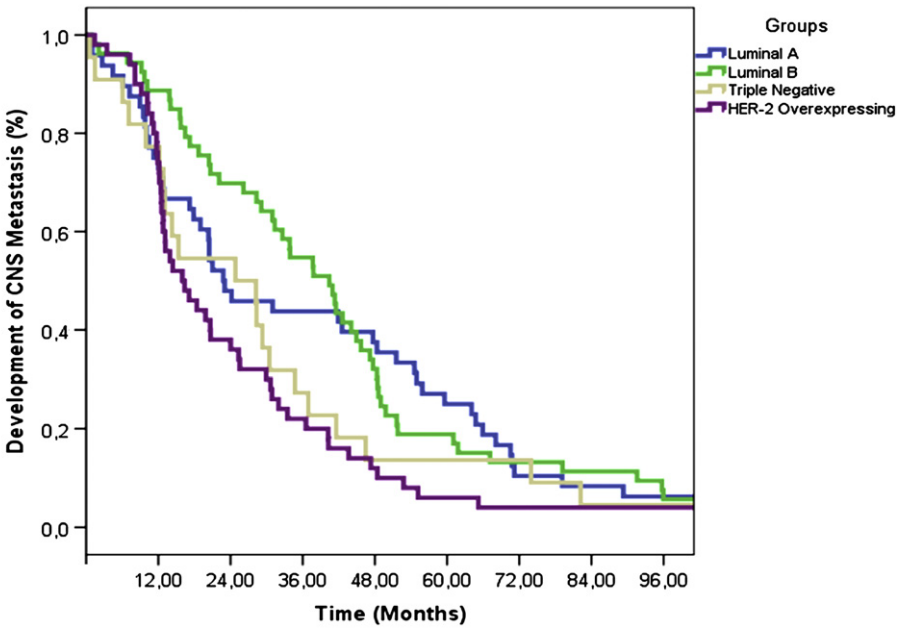
| | *n* (%) | Median survival time after CNS metastasis (months) | *p* |
|---|---|---|---|
| Age at diagnosis of CNS metastasis | | | |
| ≤47[a] | 129 (49.8) | 8.1 | 0.60 |
| >48 | 130 (50.2) | 7.4 | |
| Diagnosis of CNS metastasis | | | |
| 1995–2000 | 36 (13.9) | 6.8 | 0.96 |
| 2001–2005 | 108 (41.7) | 8.1 | |
| 2006–2010 | 115 (44.4) | 7.8 | |
| Nature of CNS metastasis | | | |
| Solitary | 53 (22.4) | 25.5 | <0.001 |
| Multiple | 184 (77.6) | 6.8 | |
| Location of metastasis | | | |
| Leptomeningeal | 22 (8.8) | 8.1 | 0.17 |
| Parenchymal | 229 (91.2) | 5.8 | |
| Number of metastatic site | | | |
| 1[b] | 32 (14.1) | 13.7 | 0.003 |
| 2 | 90 (39.6) | 7.8 | |
| 3 | 66 (29.1) | 5.1 | |
| 4 | 39 (17.2) | 4.0 | |
| Surgey for CNS metastasis | | | |
| Yes | 32 (13.0) | 21.7 | 0.001 |
| No | 215 (87.0) | 7.1 | |
| Radiotherapy for CNS metastasis | | | |
| Yes | 236 (94) | 8.1 | <0.001 |
| No | 15 (6.0) | 2.0 | |
| Chemotherapy after CNS Metastasis | | | |
| Yes | 159 (75.4) | 10.2 | <0.001 |
| No | 52 (24.6) | 2.0 | |
| First-line chemotherapy after CNS metastasis | | | |
| Monotherapy | 58 (41.4) | 7.4 | 0.009 |
| Combinations | 82 (58.6) | 12.1 | |
| Anti-HER-2 therapy after CNS metastasis[c] | | | |
| Yes | 33 (35.9) | 15.9 | 0.004 |
| No | 59 (64.1) | 7.5 | |

[a] Median age for diagnosis of CNS metastasis.
[b] Patients with only CNS metastasis.
[c] Only HER-2 positive patients included this analysis.

### *Treatment of patients with CNS metastasis*

Whole brain radiotherapy (WBRT) was used in 94% ($n = 236$) of the patients as either initial therapy or treatment after surgery. Only 13% ($n = 32$) of the patients with solitary brain metastasis were operated for CNS metastasis.

33 patients (35.9% of HER-2 positive patients) had HER-2 targeted therapy consisting of 20 patients with trastuzumab with cytotoxic chemotherapy (vinorelbine/taxanes/cisplatin), and 13 with lapatinib plus capecitabine. Only 3 patients were treated with hormonotherapy. 75.4% ($n = 159$) received chemotherapy after CNS metastasis, whereas 24% of the patients did not get any cytotoxic therapy after CNS metastasis. Besides cisplatin plus etaposide combination being the most common chemotherapy regimen; gemcitabine, vinorelbine, capecitabine, tegafur-uracil and taxanes were also used frequently after the detection of CNS metastasis. About half of Luminal A subtype patients had uncontrolled systemic disease at the time of brain metastasis, and 20% of these patients did not receive systemic therapy after CNS involvement.

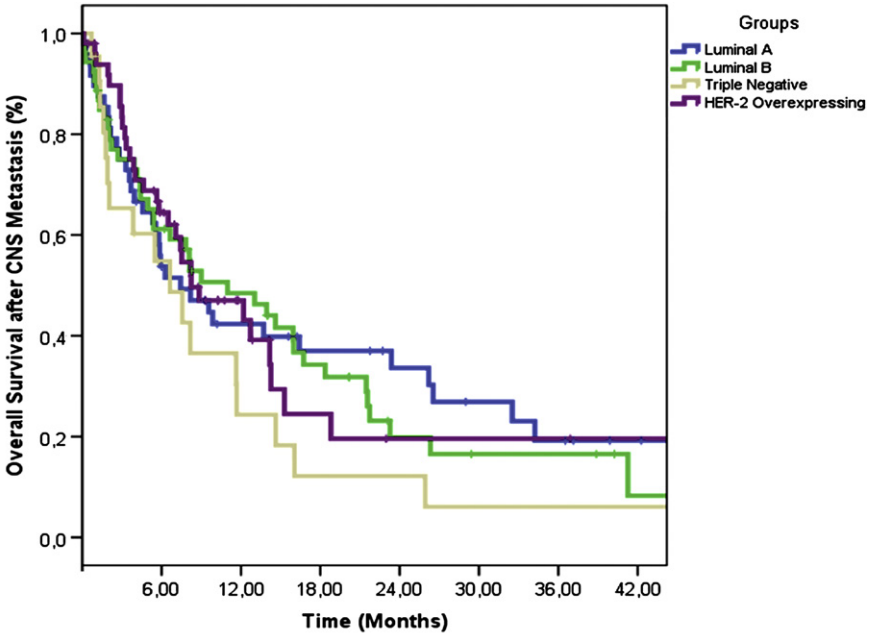



| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Luminal A | 48 | 36 | 23 | 21 | 18 | 12 | 5 | 4 | 3 |
| Luminal B | 53 | 47 | 37 | 29 | 17 | 10 | 7 | 6 | 3 |
| HER-2 Overexpressing | 50 | 37 | 19 | 11 | 6 | 3 | 2 | 2 | 2 |
| Triple Negative | 21 | 17 | 12 | 6 | 3 | 3 | 3 | 1 | 1 |

**Fig. 1.** Time period between the diagnosis of breast cancer and detection of CNS metastasis with corresponding breast cancer subtype.

*Survival analyses of the patients after the detection of CNS metastases*

191 patients (73.7%) died throughout the analysis. Median survival after the determination of CNS metastases was 7.8 months (range 0.3–131) totally, 7.4 months for luminal A, 10.9 months for luminal B, 8.2 months for HER-2 overexpressing, and 6.6 months for triple negative subtype (Fig. 2), although these differences in time intervals was not statistically significant between the subtypes ($p = 0.3$).




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Luminal A | 48 | 25 | 17 | 13 | 10 | 7 | 5 | 2 |
| Luminal B | 53 | 31 | 22 | 14 | 6 | 4 | 4 | 1 |
| HER-2 Overexpressing | 50 | 28 | 12 | 5 | 3 | 3 | 3 | 2 |
| Triple Negative | 21 | 9 | 4 | 2 | 2 | 1 | 1 | 1 |

**Fig. 2.** Overall survival time from the diagnosis of CNS metastases with corresponding breast cancer subtype.

Presence of chemotherapy after CNS involvement, surgery for CNS metastasis, solitary nature of brain metastasis, and WBRT were significantly associated with increased survival of the patients with CNS metastasis ($p < 0.001$, $p = 0.001$, $p < 0.001$ and $p < 0.001$, respectively). Patients treated with HER-2 targeted therapy after CNS metastasis showed increased survival compared to the patients who received only cytotoxic therapy ($p = 0.004$). There were no significant association between survival after CNS metastasis and age, ER, PR, HER-2 status, menopausal status, grade, and stage at the time of diagnosis, tumor histology, presence and type of adjuvant chemotherapy, presence of adjuvant hormonotherapy, presence of adjuvant radiotherapy, first site of metastasis, and type of brain metastasis (LM or parenchymal).

In multivariate Cox regression analyses, solitary nature of CNS metastasis (HR 0.4; 95% CI; 0.2–0.7; $p = 0.004$), and receiving chemotherapy for CNS metastasis (HR 0.4; 95% CI; 0.287–0.772; $p = 0.003$) were associated with increased survival; whereas multiple CNS metastases (HR 1.6; 95% CI; 1.0–2.5; $p = 0.043$), presence of a histology other than IDC (HR 2.9; 95% CI; 1,1- 7,7; $p = 0.030$) were associated with decreased survival after CNS metastasis with breast cancer.

## Discussion

Negative hormone receptor status, HER-2 overexpression, high tumor grade, the presence of lung metastases as the first site of relapse, and young age have all been determined as risk factors in the development of CNS metastases after diagnosis of breast cancer.[3,10,13–18]

HER-2 overexpressing breast cancer subtype has an aggressive clinical behavior and shorter disease-free and overall survival.[19] The relationship between trastuzumab treatment in HER-2 positive patients and the outcome of CNS metastasis is not clear. A higher CNS metastasis incidence has been reported in MBC patients treated with trastuzumab; as well as nearly one third of the patients receiving trastuzumab develops brain metastases, and this effect of trastuzumab has been related to its impermeability to blood–brain barrier.[20–22] Also, in an animal model study, HER-2 overexpression increased the outgrowth of metastatic tumor cells in the brain.[23] On the other hand, HER-2 positive breast carcinoma patients after CNS metastasis under trastuzumab treatment have prolonged survival compared to HER-2 negative patients (17.1 months *versus* 5.2 months),[24] and it has been suggested that the prolonged survival of HER-2 positive brain metastatic MBC patients under trastuzumab-based therapy is related to successful clinical control of extracranial disease of trastuzumab treatment.[22,24–27] Another study of HER-2 positive MBC patients revealed that CNS metastases develop in 48.1% of patients with trastuzumab-based therapy, and 46.6% of the patients with non-trastuzumab-based therapy; and the association between trastuzumab therapy and subsequent CNS metastases (either brain parenchyma or LM) is not significant.[28] But, trastuzumab therapy after the diagnosis of CNS metastasis in HER-2 positive breast cancer patients was found to have a significant association with survival benefit after CNS involvement compared to patients who had never received or completed trastuzumab started before the CNS metastasis diagnosis.[29] In the current study, 59.9% of patients were HER-2 positive subtype, and approximately half of these patients had been treated with trastuzumab plus chemotherapy for distant or locoregional recurrence before the detection of CNS metastasis.

Lapatinib is another option for treatment of metastatic HER-2 positive breast tumors that have been progressed under trastuzumab therapy.[30] Also, lapatinib is the first HER-2 directed drug to be validated in a preclinical model for activity against brain metastases of breast cancer.[31] A small phase II trial ($n = 39$) of lapatinib for patients who developed CNS disease on trastuzumab revealed that partial response by RECIST observed in 2 patients and 5 patients remain stabile for $\geq$ 16 weeks and suggested that lapatinib can penetrate the central nervous system.[32]

In this study, the survival time after CNS metastases was longer than the results of some historical studies conducted in late 1970's and early 1990's(7.8 months *versus* 4 months).[6,33] But, survival after CNS metastasis in patients with luminal B and HER-2 overexpressing subtypes of the current study were relatively short (10.9 and 8.2 months) compared to the data from the studies showing a positive correlation betweeen trastuzumab treatment and survival after brain metastasis ranging between 11.6 and 17.1 months.[24,26,27] This finding might be due to lack of anti-HER-2 therapy in about half of patients after local treatment of CNS metastasis in this study. Further prospective studies for the treatment choices of patients who developed CNS metastasis while on trastuzumab therapy are required.

Triple negative breast cancer is a distinct breast cancer subtype with more chemosensitive nature, bad prognosis, early relapses or recurrences, early CNS metastasis, and short survival.[9,34–36] Dawood *et al*. documented that patients with non-metastatic triple negative breast tumors have higher rate of early CNS metastasis, and the median survival time after brain metastasis of entire triple negative patient group is only 2.9 months, but median survival time after CNS relapse is 5.8 months if the CNS metastasis was the first site of recurrence (35). Also, in a survival analysis of 805 MBC patients, 126 of whom having CNS metastasis, 37% of the triple negative breast cancer patients developed CNS metastasis, and the median survival after CNS metastasis for triple negative patients was 3.4 months.[14] In another study the median survival of triple negative breast cancer patients after CNS metastasis was reported as 4.0 months.[24] In the present study, 22 (13.3%) of 172 patients had CNS relapse as the first site of recurrence and the triple negative group had the shortest median survival (6.6 months) after CNS metastasis although statistically not significant probably due to the limited number of triple negative MBC patients.

Despite the clinical behavior of luminal A subtype and the knowledge of women with hormone receptor positive breast cancer having a better prognosis due to slower growth rate than receptore-negative tumors;[37] in the current study the survival after CNS metastasis of the Luminal A subtype was relatively shorter compared to HER-2 positive subgroups. Also, median time period between the diagnosis of breast cancer and the development of CNS metastasis for this group was less than all other three subtypes. In consistent with our findings, Nam et al reported that survival from brain metastasis for Luminal A tumors was as low as for triple negatives.[14] Also, bone and soft tissue metastases rather than visceral involvement are more frequently seen in hormone receptor positive breast cancer.[38]In this study, a considerable number of Luminal A subtype had uncontrolled systemic disease at the time of brain metastasis, while 20% of Luminal A group did not receive systemic therapy after CNS involvement. It has been suggested that this short survival observed in the luminal A group after the CNS involvement was related to occurrence of brain metastasis in very late era of the disease, and the probable consequence of lack of systemic therapy. Recently, Niwinska et al showed that using systemic treatment following WBRT significantly prolongs the survival after brain metastasis in breast cancer patients with luminal A, luminal B and HER-2 tumors, as well as anti-HER-2 treatment has provided a survival benefit, but any significant survival difference between systemic treatments *versus* no treatment for triple negative patients is not detected.[12]

In summary, in spite of development of new therapeutic agents, improvement of medicine, modern surgical and radiotherapy techniques; CNS metastasis is still a continuing problem for breast

cancer patients. Although we did not find any significant difference between four breast cancer subtypes in terms of survival after CNS metastasis; the triple negative breast cancer patients with CNS metastasis had a trend of shorter survival than the other subgroups. Underlying molecular mechanisms related with breast cancer subtypes for development of central nervous system metastasis may provide a better targeted therapy options in the future and may improve survival after CNS metastasis for MBC.

## Conflict of interest

None declared.

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