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EDITORIAL

Prognostic factors of breast cancer brain metastasis

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Abstract

In this editorial we comment on the article by Chen *et al* published in the recent issue of the *World Journal of Clinical Oncology*. Brain metastasis is one of the most serious complications of breast cancer and causes high morbidity and mortality. Brain metastases may involve the brain parenchyma and/or leptomeninges. Symptomatic brain metastases develop in 10%-16% of newly recognized cases each year, and this rate increases to 30% in autopsy series. Depending on the size of the metastatic foci, it may be accompanied by extensive vasogenic edema or may occur as small tumor foci. Since brain metastases are a significant cause of morbidity and mortality, early diagnosis can have significant effects on survival and quality of life. The risk of developing brain metastases emerges progressively due to various patient and tumor characteristics. Patient variability may be particularly important in the susceptibility and distribution of brain metastases because malignant blood must cross the brain barrier and move within the brain parenchyma. Some characteristics of the tumor, such as gene expression, may increase the risk of brain metastasis. Clinical growth, tumor stage, tumor grade, growth receptor positivity, HER2 positivity, molecular subtype (such as triple negative status, luminal/nonluminal feature) increase the risk of developing breast cancer metastasis. Factors related to survival due to breast cancer brain metastasis include both tumor/patient characteristics and treatment characteristics, such as patient age, lung metastasis, surgery for brain metastasis, and HER2 positivity. If cases with a high risk of developing brain metastasis can be identified with the help of clinical procedures and artificial intelligence, survival and quality of life can be increased with early diagnosis and treatment. At the same time, it is important to predict the formation of this group in order to develop new treatment methods in cases with low survival expectancy with brain metastases.

Key Words: Breast cancer; Brain metastasis; Prognosis; Artificial intelligence; Clinicopathological features

Core Tip: Breast cancer is still the most common cancer in women. Breast cancer is the second most common cancer causing brain metastasis. In breast cancer, the first metastasis occurs to the brain with a rate of 12%. In recent years, the prognosis of breast cancer-related brain metastases has improved, and survival and the patient's quality of life have increased, thanks to both changes in medical treatments and technological advances in radiotherapy. For this reason, early diagnosis of cases is very important. At the same time, survival is not the same in every case of brain metastasis. Identifying cases with low survival seems to be very important in paving the way for studies to change treatment strategies.

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INTRODUCTION

Breast cancer is the most common cancer in women regardless of race and ethnicity. 30% of newly diagnosed patients have breast cancer, and 15% of cancer deaths are caused by breast cancer[1]. While symptomatic brain metastases develop in 10%-16% of newly diagnosed breast cancer patients each year, this rate is 30% in autopsy series[2,3]. In cases diagnosed with breast cancer that develop brain metastases, survival rates may be as low as 2-9 mo despite treatment. Surgical resection, whole brain radiotherapy, stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), chemotherapy and targeted therapies can improve outcomes in these patients[4,5]. Identifying prognostic factors associated with breast cancer brain metastasis may help identify patients at risk. According to studies, some characteristics of the patient and the tumor have been shown to increase the risk of breast cancer. In most breast cancers, brain metastases occur 2-3 years after initial diagnosis, and only 20% of patients survive after 1 year[6]. After breast cancer develops, some patient, tumor and treatment characteristics that affect the prognosis regarding survival have been determined in studies. If the patient's prognosis can be predicted after developing breast cancer, different treatment options may come to the fore in patients with good prognosis/bad prognosis.

In this editorial we comment on the article by Chen *et al*[7] published in the recent issue of the *World Journal of Clinical Oncology*. Brain metastasis is one of the most serious complications of breast cancer and causes high morbidity and mortality. Brain metastases may involve the brain parenchyma and/or leptomeninges. Symptomatic brain metastases develop in 10%-16% of newly recognized cases each year, and this rate increases to 30% in autopsy series. Depending on the size of the metastatic foci, it may be accompanied by extensive vasogenic edema or may occur as small tumor foci. Since brain metastases are a significant cause of morbidity and mortality, early diagnosis can have significant effects on survival and quality of life. The risk of developing brain metastases emerges progressively due to various patient and tumor characteristics. Patient variability may be particularly important in the susceptibility and distribution of brain metastases because malignant blood must cross the brain barrier and move within the brain parenchyma. Some characteristics of the tumor, such as gene expression, may increase the risk of brain metastasis. Clinical growth, tumor stage, tumor grade, growth receptor positivity, HER2 positivity, molecular subtype (such as triple negative status, luminal/nonluminal feature) increase the risk of developing breast cancer metastasis. Factors related to survival due to breast cancer brain metastasis include both tumor/patient characteristics and treatment characteristics, such as patient age, lung metastasis, surgery for brain metastasis, and HER2 positivity. If cases with a high risk of developing brain metastasis can be identified with the help of clinical procedures and artificial intelligence, survival and quality of life can be increased with early diagnosis and treatment. At the same time, it is important to predict the formation of this group in order to develop new treatment methods in cases with low survival expectancy with brain metastases.

PROGNOSTIC FEATURES IN BREAST CANCER BRAIN METASTASIS

When we look at the literature, many prognostic features in breast cancer have been investigated due to the high incidence of breast cancer. If we look at the prognostic factors related to brain metastasis; We can examine it in two groups: prognostic factors that increase the risk of developing brain metastasis and prognostic factors that affect survival after the development of brain metastasis.

Unlike other metastasis sites, brain metastasis is usually observed after a latent period after diagnosis in breast cancer, and this can be explained by the blood-brain barrier. The blood-brain barrier is a complex structure consisting of endothelial cells, tight junctions, basement membrane, pericytes, astrocytes, microglia, enzymes and transporters. It controls the permeability of the brain to macromolecules and is also involved in the transmission of signals and maintenance of central nervous system homeostasis. For this reason, biological pathways and regulatory molecules formed across the blood-brain barrier are also very important in preventing brain metastasis due to breast cancer[8]. In addition to treating patients with brain metastases, preventing brain metastases due to the primary tumor is also an important clinical goal. Such prevention would require detecting circulating brain-tropic cancer cells before extravasation.

Liquid biopsy is a potential screening tool for the detection of such cells in circulation[9].

Local therapeutic approaches such as surgery and radiotherapy have proven effective for metastatic brain tumors. Systemic treatments to control extracranial disease are developing. However, specific treatments targeting brain metastases in breast cancer patients have not been established, and therefore the prognosis of such patients remains poor. Identification of the cellular and molecular mechanisms underlying brain metastasis of breast cancer will likely provide a basis for the prevention or treatment of such diseases. Breast cancer is divided into several subtypes based on the expression status of human epidermal growth factor receptor 2 (HER2) and estrogen (ER) and progesterone (PR) receptors by immunohistochemical staining or gene expression profiles. These breast cancer subtypes have been found to have different gene signatures, rely on different signaling pathways for metastasis, and show different metastatic site preferences. Patients with HER2-positive breast cancer or triple-negative (HER2− ER− PR−) breast cancer (TNBC) have a higher risk of brain metastasis compared with those with the luminal subtype of breast cancer (ER+ or PR+). Therefore, the frequency of brain metastasis is as high as 20% to 30% in HER2-positive breast cancer and TNBC, but is less than 10% in luminal breast cancer[10].

In a meta-analysis conducted by Hackshaw *et al*[11], 25 studies on this subject and 4097 HER-2 positive breast cancer brain metastasis patients were evaluated. The time between breast cancer diagnosis and the development of brain metastasis was found to be associated with early age, negative hormone receptors, large tumor size, high tumor grade, and not receiving anti-HER-2 treatment. When looking at survival due to brain metastasis, having < 3 metastatic lesions and receiving a local treatment for brain metastasis (SRS, SBRT or surgery) increased survival. At the same time, the longest survival was observed in those treated with trastuzumab and lapatinib or trastuzumab and pertuzumab.

In a study conducted by Leone *et al*[12], prognostic factors were examined in 42 patients who developed brain metastases due to breast cancer and underwent craniotomy. Median survival after brain metastasis develops is 1.33 years. While the only factor affecting the time from breast cancer diagnosis to brain metastasis development is tumor stage, the most important factor affecting survival after brain metastasis is age.

In a study conducted by Castanede *et al*[13] with 215 cases diagnosed with early stage breast cancer, prognostic factors affecting survival due to brain metastasis were investigated. Prognostic factors were found to be nonluminal status, presence of extracrainal metastasis, ≤ 15 mo between breast cancer diagnosis and brain metastasis development, presence of > 3 brain metastasis lesions, and high-grade tumor.

In the literature review by Rostami *et al*[14]; 106 articles and 14599 patients including breast cancer brain metastasis cases were evaluated. Factors affecting prognosis are tumor grade and size, presence of multiple metastases, presence of extracranial metastases, triple negative status, HER2 positivity and Karnofsky score.

Nie *et al*[15] made prognosis prediction with LASSO Cox regression analysis. According to this analysis, the presence of lymph node metastasis, molecular subtype, tumor size, history of chemotherapy and radiotherapy, and the presence of lung metastasis were found to be important variables related to the development of brain metastasis. Li *et al*[16] made prognosis prediction in cases of breast cancer brain metastasis using machine learning method. Among the evaluated algorithms, they reached the highest accuracy rate with the XGBoost model. According to the study, surgery increases survival in HER2+ and triple-negative cases.

CONCLUSION

Breast cancer is the most common cancer in women, and when autopsy series are included, the rate of brain metastasis increases up to 30%. If patients with a high risk of brain metastasis due to breast cancer can be identified, the risk of developing brain metastasis can be reduced and survival can be increased, perhaps with prophylactic brain irradiation, as in small cell lung cancer. Using artificial intelligence, the risky patient group can be predicted through studies with a larger number of patients.

In cases with a high risk of developing brain metastasis and a poor prognosis after the diagnosis of brain metastasis, more effective treatment strategies can be determined if the molecular and cellular mechanisms affecting this can be revealed.

FOOTNOTES

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