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Effect of molecular subtypes on radiotherapy response in patients with breast cancer brain metastasis

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ABSTRACT

Objective: This study aimed to investigate survival and the response to radiotherapy (RT) among patients with molecular subtypes of breast cancer brain metastases.

Patients and Methods: We retrospectively analyzed the data of 139 breast cancer patients with brain metastases treated with whole-brain radiotherapy (WBRT) or focal brain treatment (FBT) between 2006 and 2019. Overall survival (OS) and brain metastasis progression-free survival (BMPFS) were calculated from the first RT until death or the last follow-up. Survival analyses were performed using the Kaplan–Meier method. Prognostic factors were evaluated using the Cox proportional hazard model.

Results: Twenty three (16.5%), 77 (55.4%), 14 (10.1%), and 25 (18%) patients were diagnosed with triple-negative, HER-2 (+), luminal-like A, and luminal-like B breast cancer, respectively. Of 139 patients, 66 (47.8%) underwent FBT, and 73 (52.5%) underwent WBRT. While the most preferred fraction was 10*300 Gy in WBRT, doses of 15-25 Gy in 1-5 fractions were preferred in local RT. We observed that age, Karnofsky performance scale (KPS) score, initial RT technique, extracranial disease, number of brain metastases impacted OS and BMPFS.

Conclusion: Breast cancer brain metastasis is a different, complex, and challenging disease based on the molecular subtype of the tumor, despite various local treatments. Therefore, appropriate and tailored treatment approaches should be considered for the different molecular subtypes.

Keywords: Breast cancer, Molecular subtype, Brain metastasis, Radiotherapy, Survival outcomes

1. INTRODUCTION

Metastatic breast cancer (MBC) is the second most common cause of brain metastases (BM) among solid malignancies [1, 2]. Approximately 10-30% of all breast cancer patients develop breast cancer brain metastases (BCBM) with a median survival of 14 months [3-5].

Breast cancer is divided into molecular subtypes depending on the presence or absence of the estrogen receptor (ER) and human epithelial growth factor receptor-2 (HER-2). Frequency and incidence of BCBM change based on molecular subtypes such as luminal A and luminal B type, HER-2 type, and triple-negative (TN) type; therefore treatment strategies need to be changed depending on the subtype [6, 7]. Despite recent advances in systemic treatment, HER-2 and TN subtypes still exhibit shorter survival rates than luminal subtypes [8]. In addition, while the frequency of brain metastasis development in luminal subtypes is <10%, this rate varies between 20%-30% in TN and HER-2 positive subtypes [9].

Current treatment options for patients with BCBM include surgical resection, focal brain treatment (FBT) (surgery or RT), whole-brain radiation therapy (WBRT), chemotherapy, and targeted therapy. The National Comprehensive Cancer Network (NCCN) treatment guidelines for brain metastasis are based on the number of metastases. Tumor removal, WBRT, and FBT are recommended in patients with 1 – 3 limited metastatic lesions, but WBRT or FBT are recommended for patients with more than three lesions [10-12]. The response rates to treatment in brain metastases vary according to the number of metastases, location, performance status, and subtypes [13]. To prevent systemic progression and the development of new metastases, primary systemic treatments, including hormonal therapies, targeted

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agents, and immunotherapies, are applied in combination or sequentially with versatile treatment modalities [14].

In this retrospective study, we aimed to investigate the factors affecting oncological outcomes including; overall survival (OS), brain metastasis-free progression-free survival (BMPFS), association between breast cancer subtype, and intracranial recurrence patterns in patients who developed brain metastasis at the time of admission or during follow-up after adjuvant radiotherapy for breast cancer.

2. PATIENTS and METHODS

The study included one hundred and thirty-nine breast cancer patients who developed brain metastases in their follow-up after adjuvant breast cancer RT or who had brain metastases at admission and who had undergone WBRT or FBT between 2006 and 2019. This study was approved by the the Institutional Review Board of Kartal Dr. Lütfi Kırdar City Hospital (Approval number 2018/514/122/5 on 30.01.2018). This retrospective design exempted this study from the requirement of obtaining written informed consent from the patients.

Patient Characteristics

Women older than 18 years were eligible for this study. All the patients were diagnosed with breast cancer and brain metastases. Male patients were excluded from this study. ER status, progesterone receptor (PR) status, and HER-2 expression and/or amplification status were collected for patients based on primary and/or metastatic breast cancer pathology analysis. Breast cancer subtypes were classified according to the criteria described by St. Gallen in 2015. Luminal A (ER+/HER2−, grade 1-2, Ki 67 ≤ 20% and /or low mitotic index), luminal B (ER+/ HER2+, grade 3, Ki 67 > 20% or high mitotic index), and HER-2 (HR−/HER2+) and triple-negative (TN) (ER−, PR−, HER-2 −) [15]. Demographic patient data (age, date of brain metastasis diagnosis, the number of brain metastases, Karnofsky performance scale (KPS) score at initial RT, extra-cranial disease, tumor molecular subgroup, RT type, and RT dose delivered) were collected from the electronic medical records. Patients with metastatic breast cancer treated with more than one course of brain metastasis irradiation were identified, and the clinical outcomes of re-irradiation in these patients were investigated.

Radiotherapy

Patients diagnosed with primary breast carcinoma that metastasized to the brain and treated with WBRT, FBT, or both were included. The clinical treatment volume (CTV) was determined as the brain parenchyma, and the margin was defined as the planned treatment volume (PTV). In single or oligometastatic lesions, RT was planned without margin for gross treatment volume in the post-surgical cavity or primer radiosurgery applications. Radiosurgery, (primary or postoperative cyberKnife and Gamma-Knife), and linac-based planning systems were applied as local treatments.

Statisticsal Analysis

Clinical outcomes were determined as primary endpoint OS and secondary endpoint as BMPFS. OS was defined as the time from the initial brain metastasis diagnosis to the time of death or the last follow-up. At the same time, BMPFS was defined as the time from the initial brain metastasis diagnosis to the time of BM progression. Statistical analysis was conducted using the SPSS 23 (version 23) program. Frequency distribution (number and percentage) for categorical variables and descriptive statistics (mean, standard deviation, median, minimum, and maximum) were applied for numerical variables. One-way analysis of variance (ANOVA) was used to determine whether there was a difference between more than two groups. Kaplan-Meier analysis was used to examine the differences in patient survival according to age, presence of metastasis at baseline, and subtypes. The significance level was accepted as $p<0.05$.

3. RESULTS

From 2006 to 2019, 139 patients diagnosed with breast cancer, who received RT for brain metastasis during their follow-up or admission, or who received a second course of WBRT or FBT with cranial recurrences and new lesion development during follow-up were included. Patient characteristics are summarized in Table I. The median age at diagnosis of BM was 54 years (range, 30-94). The median follow-up period from the initial breast cancer diagnosis was 83 months (range, 45.8-120). The distribution of patients according to subtypes was TN 16.5% (23), HER-2 (+) 55.4% (77), luminal-like A 10.1% (14), luminal-like B 18%. Brain metastases represented the only intracranial metastases in 82 patients (59 %), while 14 patients (10.1 %) had both brain and systemic metastases. The median KPS score before the initial RT was 90 (range, 70-100). The median elapsed time until progression after the initial RT was ten months (range, 1-116). KPS median before the second-course RT was 90 (range, 60-100). After the first RT, local progression was observed in 50 patients (38.5%), distant intracranial metastasis developed in 59 patients (45.4%). The median elapsed time until progression after the second-course RT was nine months (range, 2-24). Before the third course RT, the median KPS was 90 (range, 60-90). The median elapsed time until progression after the third course of RT was six months (range, 1-12). After the third course RT, five patients (3.5%) developed distant intracranial metastasis, and three patients (2.1%) had an intracranial progression. The median KPS before the fourth course RT was 80 (range, 70-90). In total, WBRT was administered to 97 of 139 patients, FBT to 128 lesions in 139 patients, second-course WBRT in 4 patients, and second-course FBT in 2 patients.

Treatment outcomes

The median OS was 71 months (95% CI, 46.2–95.7 months), and the median BMPFS was 14 months (95% CI, 5.3–22.6 months). The difference between overall survival and the presence of metastasis at admission according to subtype was not statistically significant ($p>0.05$). The median overall survival according to HER-2 (+), TN, luminal A and luminal B subtypes was 146, 106, 101, and 59 months, respectively (Figure 1). The BMPFS analysis showed no statistically significant difference between subtypes, age groups, and the presence of metastasis at baseline in terms of progression-free survival time after cranial metastasis ($p>0.05$).

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Table 1. *Characteristics of patients*

	n	(%)
Patients	139	(100)
The median age in years at brain metastasis diagnosis	54 (range, 26-94)	
Median follow-up in months	83 (range, 45.8 – 120)	
Initial T stage		
< 2 cm	14	(11.1)
2-5 cm	62	(44.1)
> 5 cm	59	(42)
Unknown	4	(2.8)
Menopause		
Premenopausal	79	(56.8)
Postmenopausal	60	(43.2)
Histology		
Invasive ductal carcinoma	124	(89.2)
Invasive lobular carcinoma	6	(4.3)
Other	9	(6.5)
Estrogen receptor status		
Positive	74	(53.2)
Negative	65	(46.8)
Progesterone receptor status		
Positive	68	(48.9)
Negative	71	(51.1)
HER-2 status		
Positive	68	(48.9)
Negative	24	(17.3)
Unknown	47	(33.8)
Subtype		
Basal	23	(16.5)
Luminal A	14	(10.1)
Luminal B	25	(18)
HER-2	77	(55.4)
Chemotherapy		
Yes	131	(94.2)
No	8	(5.8)
Targeted therapy n %		
Yes	77	(56.2)
No	34	(24.8)
Unknown	26	(19)
Extra-cranial disease		
Yes	58	(40.6)
No	43	(30.1)
Unknown	38	(27.3)
Radiation therapy		
Initial whole breast radiotherapy	72	(52.1)
Initial focal brain treatment	66	(47.8)
Number of brain metastasis		
1-4	88	(70.6)
> 4	51	(29.4)

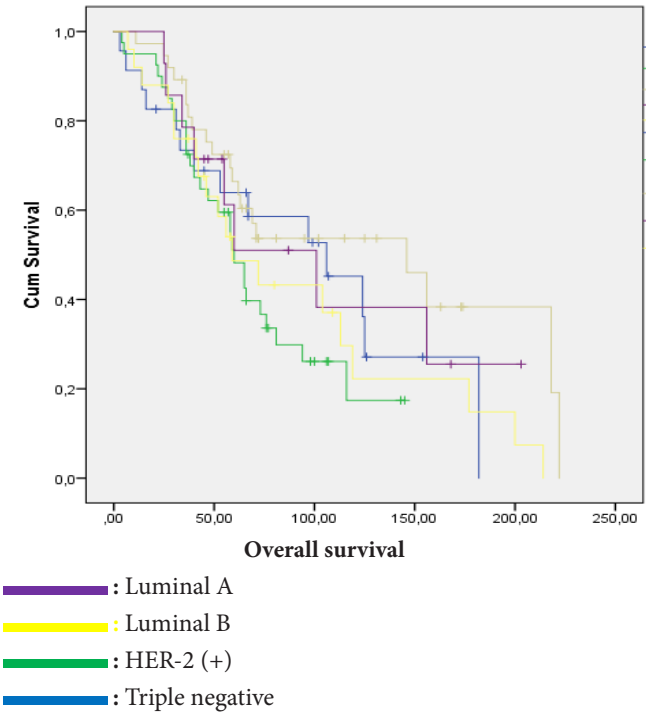

Figure 1. *Overall survival among patients according to molecular subtypes*

Of the 139 patients examined, 73 (52.5%) received WBRT for the brain metastasis, and 66 (47.8%) received FBT. WBRT was delivered at a median dose of 30 Gy in ten fractions. Doses of 15-25 Gy in 1-5 fractions were preferred for FBT. After the first RT, local progression was observed in 50 patients (38.5%), and distant intracranial metastasis developed in 59 (45.4%) patients. As secondary-course RT, FBT was received in 50 patients (38.5%), WBRT to 20 patients (15.3%), and second-course WBRT to 2 patients (1.5%). After the second-course RT, four patients (3%) underwent cranial metastasectomy. Therefore, WBRT was administered to 97 of 139 patients, FBT to 128 lesions in 139 patients, second-course WBRT in 4 patients, and second-course FBT to 2 patients. The change in the time elapsed until the progression after radiotherapy applications according to molecular subtypes did not show a statistically significant difference ($p>0.05$). Eighty-nine patients (64%) died due to brain metastasis during follow-up after treatment. While the highest mortality rate was observed in the HER-2 (+) subtype with 28 patients (31.8%), the lowest mortality rate was in the luminal-like A subtype with eight patients (9.1%).

4. DISCUSSION

The risk of developing brain metastasis is estimated to be as high as 25% among patients with breast cancer, with a median time of brain metastasis occurrence 2–3 years after the initial breast cancer diagnosis [16]. High tumor burden, HER-2 positivity, hormone receptor negativity, young age, and the presence of visceral organ metastasis are important

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predictive factors for the development of brain metastasis in breast cancer [17-21]. However, KPS is known to be a critical prognostic factor for demonstrating treatment effectiveness and response [21, 22]. In our study, the median KPS values before the initial RT, before the second-course RT, before the third course RT and before the fourth course RT were 90, 90, 90, and 80, respectively. Treatment of brain metastasis according to location, number of lesions, performance status, and biological subtype also makes treatment complex and challenging [23]. Although, the development and treatment of breast cancer brain metastasis involve many difficulties, FBT or WBRT, surgery, and chemotherapy are used in combination or separately with targeted agents and immunotherapy. WBRT combined with FBT showed a better survival advantage than WBRT alone. However, the superiority of salvage WBRT and FBT over FBT alone had not been demonstrated [24-29]. Although, there have been many improvements in the treatment of breast cancer patients diagnosed with brain metastasis over the years, the development and causes of brain metastasis according to molecular subtypes are still unknown [30]. In our study, the change in the time elapsed until the progression after radiotherapy applications according to molecular subtypes, did not show a statistically significant difference.

Breast cancer brain metastasis patients with luminal A and luminal B had the best OS, TN had the worst OS [7, 31-35]. In addition, the response to RT varies according to the subtype of BCBM. In two different studies according to subtypes, survival differences were stated as 7.3 months/7 months in TN subtype, 17.9 months/23 months in HER2 (+) subtype, 10 months/16 months in luminal-like A subtype, and 22.9 months/26 months in luminal-like B [31, 36]. In our study, the median OS according to the subtypes HER-2 (+), TN, luminal A and luminal B were 146, 106, 101, and 59 months respectively.

Hicks et al., stated that there is a risk of brain metastasis in the presence of visceral metastasis in the HER-2 subtype and TN subtype, independent of the stage [37]. Generally, the response to treatment in HER-2 (+) subtype were better than HER-2 negative. The median survival with local RT in HER-2 (+) brain metastasis was 31.3 months, it was 14.1 months for HER2 (-) disease [38]. The SEER database study by Wang et al., reported that patients with luminal A (HR+/HER-2 negative) subtype had a high incidence of brain metastasis and also showed that the HER-2 subtype had a more favorable cancer-specific survival rate [39-45].

Studies stated that when WBRT was used together with systemic therapy, it increased the effectiveness of the drug in brain metastasis and the response rates to treatment by 4-38% [46-49]. Although, we did not evaluate the effectiveness of specific chemotherapy together with RT in this study, 94.2% of the patients received neoadjuvant/adjuvant/palliative chemotherapy. According to a study investigating the efficacy of trastuzumab with RT, an increased level of trastuzumab (a monoclonal humanized antibody approved for the treatment of HER-2 (+) breast cancer) was observed in the cerebrospinal fluid after RT when compared with the level before RT [50-52]. Lapatinib (a dual HER-2 and epidermal growth factor receptor (EGFR) inhibitor) is another anti-HER-2 agent used in breast cancer treatment, similar to trastuzumab. However, studies have shown that a single dose of lapatinib has a higher complete response rate than local RT alone [53]. WBRT and/or FBT with targeted agents such as trastuzumab and lapatinib provide better local and distant control [54]. Although, there is no survival advantage in combined use of lapatinib with FBT over the single use of FBT, many studies have shown that it increases the median survival [54-57]. In retrospective series, studies have shown that lapatinib with FBT has a survival advantage [58].

The most significant limitation of our study is its retrospective design. In addition, HER-2 target therapy and chemotherapy information are not known in detail, and its association with RT has not been investigated. Although, the presence of metastasis on admission was evaluated in our study, visceral and other organ metastases were not assessed. However, visceral metastasis is a prognostic determinant of breast cancer brain metastasis and determines poor prognosis independent of subtype [59].

Conclusion

The response to treatment and disease-related survival vary significantly according to the molecular subtypes of breast cancer brain metastasis. Molecular subtype is an independent predictor of OS, regardless of whether the patient received any local or systemic treatment. With the contribution of RT and new agents, the survival rate of patients with HER2 (+) subtype increased when compared to that of the other subtypes. Breast cancer brain metastasis is a different, complex, and challenging disease, and tailored treatment approaches based on the molecular subtype should be considered to improve outcomes.

Compliance with Ethical Standards

Ethical approval: The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethical Board (Approval number: 2018/514/122/5 date: 30.01.2018).

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Conflict of Interest: The authors have no conflicts of interest to declare.

Author Contributions: AAE and MFE : Concept and design of the study, AAE : Data acquisition, MFE : Statistical analysis, AAE and MFE : Literature Review, MFE and AAE: Drafting and Writing. Both authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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