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Breast Radiotherapy: A Potential Risk Factor for Resistant Clone Development in Patients with Brain Metastasis

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ABSTRACT

Objective: The human brain is a frequent site of breast cancer metastasis. The various therapeutic approaches for treating brain metastases include surgical intervention, stereotactic radiosurgery (SRS), and whole-brain radiotherapy (WBRT). However, the literature on the association between prior breast RT and the effectiveness of intracranial RT subsequent to treatment is scarce. The present study, therefore, aimed to understand the association between previous breast RT and intracranial progression-free survival (iPFS).

Material and Methods: In the present study, the relationship of epidemiological, pathological, and clinical features, especially previous breast RT, with iPFS was explored in the patients diagnosed with human epidermal growth factor receptor 2-positive breast cancer along with brain metastasis. These patients did not undergo surgery for brain metastasis and received WBRT/SRS instead.

Results: Fifty-one patients were included in the present study. The median age of these patients was 46 years. Among the included patients, 20 patients had previously undergone whole breast or chest wall RT. In 19 patients, SRS was utilized rather than WBRT. The iPFS was significantly shorter in patients who had previously received RT for the primary lesion compared to those who had not received RT (mPFS: 7.96 vs. 14.56 months, p=0.002, hazard ratio: 3.06, confidence interval: 1.52-6.12). No relationships of iPFS with the treatments used prior to RT, type of RT, sites of metastasis during RT, systemic therapy administered after RT, and status of *de novo* metastatic/recurrent disease were noted.

Conclusion: Patients who had undergone previous RT to the locoregional region exhibited significantly poorer iPFS following the RT performed for brain metastasis.

Keywords: Breast radiotherapy; HER-2 positive breast cancer; brain metastasis

INTRODUCTION

The human brain is a frequent site of metastasis in solid organ malignancies, and approximately 25% of the patients with cancer eventually develop brain metastases.[1] The most common tumor types that tend to metastasize to the brain include malignant melanoma, lung cancer, and breast cancer.[2] After the development of brain metastasis, the overall survival (OS) duration is generally less than 12 months.[3] Immun checkpoint inhibitors and certain tyrosine kinase inhibitors have demonstrated high efficacy in treating brain metastases.[4-8] These treatments have led to improved survival rates, particularly among patients with lung cancer and malignant melanoma, along with brain metastases.

Breast cancer is the most commonly diagnosed cancer among women worldwide and the second leading cause of cancer-related deaths after lung cancer.[9] Despite the advances in

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systemic therapy for breast cancer, which have significantly improved the survival rates of patients, a corresponding increase has been noted in the incidence of brain metastases.[10-13] Brain metastases have been observed more frequently in patients with hormone receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-positive breast cancer.[14] While certain studies have indicated that trastuzumab treatment delayed the development of brain metastases, a previously reported meta-analysis revealed an increased probability of brain metastasis at the time of the first relapse.[15,16]

The standard treatment options for patients with breast cancer who develop brain metastasis include surgery, stereotactic radiosurgery (SRS), and whole-brain radiotherapy (WBRT).[17]

Surgical interventions for metastasis are prioritized less and are recommended mainly in cases of advanced disease where systemic control cannot be achieved or in patients who are unable to undergo surgery. In such patient populations, whole-brain RT or SRS are often used as the primary treatment options, depending on the number of metastatic lesions detected in the brain. However, not all patients respond to RT, and previous studies have explored the factors responsible for this primary resistance to RT in certain patients.[18]

In the above context, the author of the present report hypothesized that prior RT to the primary cancer site could enable the suppression of radio-sensitive clones while allowing the survival of radio-resistant clones. No study reported in the existing literature has, to the best of the author's knowledge, specifically investigated the impact of prior RT to the primary cancer site on the outcomes of the subsequent RT treatment for brain metastasis. Therefore, the present study aimed to explore the factors, including prior breast RT, that impact the effectiveness of brain RT in patients diagnosed with HER2-positive breast cancer along with brain metastasis.

MATERIAL AND METHODS

The present study was designed as a retrospective study conducted with patients who visited the outpatient clinics of Hacettepe University Oncology Hospital between January 2018 and January 2024. The inclusion criteria for the study were as follows: a diagnosis of metastatic breast cancer with positive HER2 expression, presence of brain metastasis, absence of surgical intervention for brain metastasis, and receipt of RT for brain metastasis. The exclusion criteria were as follows: the presence of brain metastasis at the time of breast cancer diagnosis, medical oncology or radiation oncology follow-up at another medical center, and lack of response evaluation imaging after RT (except for the cases in which the patient died prior to performing imaging control, which were, therefore, included in the study). The patients with five or more brain metastases received WBRT as the initial treatment modality, with a fraction dose of 3 Gy to a total dose of 30 Gy. However, for patients with less than five metastases, especially those with controlled primary cancer and no other metastasis, SRS was preferred as the treatment approach.

The clinical data (age, stage, pre/post RT anti-HER2 therapy, number of brain metastases, type of RT, and the site of metastasis during RT) and the pathological characteristics (estrogen receptor expression) of all included patients were documented, and prognostic factors were investigated, including whether a relationship existed between the time to intracranial progression-free survival (iPFS) and previous breast RT. The definition of iPFS was as follows: the duration between the initiation of RT and the radiologically confirmed intracranial progression or death.

Statistical Analysis

Statistical analysis was conducted using the IBM SPSS Statistics Version 22 (Chicago, IL, USA) software package. The relationship between various clinical factors and brain PFS was assessed based on Kaplan-Meier curves. Median survival times along with their corresponding 95% confidence intervals (CI) were reported. Cox's regression analysis could not be performed due to the limited number of patients included in the study. A p-value of less than 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Local Research Ethics Committee of the Faculty of Medicine at Hacettepe University (date: January 24, 2023, no: GO/2308). All procedures and stages of the study were conducted in compliance with the ethical principles outlined in the World Medical Association Declaration of Helsinki, which governs the inclusion of human subjects in medical research. The participants provided written informed consent.

RESULTS

Baseline Characteristics

Fifty-one patients were enrolled in the present study. The median age was these patients was 4610.52± years, and 25 of these patients had estrogen receptor-positive tumors. At the time of diagnosis, 9 among the included 51 patients had Stage 2, 12 had Stage 3, and 30 had Stage 4 disease. Among all patients, 20 had undergone whole breast/CW with or without regional RT previously, while 31 had not received locoregional

RT. All patients had received treatment with trastuzumab, while 11 had received pertuzumab, 7 had received TDM-1, and 2 had received lapatinib.

Brain metastasis was detected with a single focus in 7 patients, 2-4 foci in 12 patients, and 5 or more foci in 32 patients. SRS was performed for 19 patients, while whole-brain RT was conducted for 32 patients. At the time of brain radiation therapy, liver metastasis was detected in 12 patients, lung metastasis in 14 patients, and bone metastasis in 26 patients. After RT, eight patients received the capecitabine-lapatinib combination, 12 received TDM1, and 31 received the trastuzumab+chemotherapy±pertuzumab treatment. The basal epidemiological, clinical, and pathological characteristics of all patients are presented in Table 1.

Clinical and Pathological Characteristics of the Patients Who Received and Those Who Did Not Receive Breast RT

The mean age at diagnosis was 47.35±11.60 years for patients who received breast RT and 45.00±9.68 years for those who did not receive breast RT. The duration between the diagnosis and the development of brain metastasis was 22.46±40.35 months for patients who received breast RT and 18.10±10.14 months for those who did not receive breast RT. Estrogen receptor positivity was similar in both groups. At the time of diagnosis, 6 patients (30%) who received breast RT were classified as Stage 2, 7 (35%) as Stage 3, and 7 as Stage 4, while in the group that did not receive breast RT, 3 patients were classified as Stage 2 (9.7%), 5 as Stage 3 (16.1%), and 23 as Stage 4 (74.2%) (p=0.020). The treatments received prior

TABLE 1: Baseline characteristics of patients.

			No (%)
Age ($\overline{X}$ ± SD)		46.00±10.52	
Estrogen receptor expression Negative		Positive	25 (49)
		26 (51)	
Stage at diagnosis		2	9 (17.6)
		3	12 (23.55)
		4	30 (58.8)
Breast RT No		Yes	20 (39.2)
		31 (60.8)	
Prior anti-HER2 therapy	Trastuzumab	Yes	51 (100)
		No	0 (0)
	Pertuzumab	Yes	11 (21.6)
		No	40 (78.4)
	Ado-trastuzumab emtansine	Yes	7 (13.7)
		No	44 (86.3)
	Lapatinib	Yes	2 (3.9)
		No	49 (96.1)
Brain metastasis number		1	7 (13.7)
		2-5	12 (23.5)
		>5	32 (62.7)
Treatment after RT	Capecitabine+Lapatinib		8 (17.6)
	Ado-trastuzumab emtansine		12 (23.5)
	Trastuzumab+Cht+Pertuzumab		31 (58.8)
RT type	Stereotactic radiosurgery		19 (37.3)
	Whole brain RT		32 (62.7)
During brain RT	Liver metastasis	Yes	12 (23.5)
		No	39 (76.5)
	Lung metastasis	Yes	14 (27.5)
		No	37 (72.5)
	Bone metastasis	Yes	26 (49)
		No	25 (51)

SD: Standard deviation; RT: Radiotherapy; Cht: Chemotherapy; HER2: Human epidermal growth factor receptor 2.

to brain RT were similar in both groups. All patients received treatment with trastuzumab, while among those who received breast RT, 3 (15%) received pertuzumab, 3 (15%) received TDM-1, and 1 (5%) received lapatinib. In patients who did not receive breast RT, the usage rates of pertuzumab, TDM-1, and lapatinib prior to brain metastasis were 25.8%, 12.9%, and 3.2%, respectively, which were similar to those noted for the patients who received breast RT (p-values: 0.493, 1.000, and 1.000, respectively).

Brain-Progression Free Survival and OS

The median follow-up period in the study population was 25.10±4.82 months, and during this period, progression of brain lesions was observed in 40 patients. The median brain PFS was 11.90±0.92 months in the study population. Brain PFS was significantly shorter in patients who had received RT to the primary lesion previously, compared to the patients who had not received this treatment (mPFS: 7.96 months vs. 14.56 months, p=0.002, HR: 3.06, CI: 1.52-6.12; the relationship between the iPFS of patients who received and did not receive adjuvant RT is depicted in Figure 1). No significant relationship was noted between the PFS of brain lesions and the treatments used prior to RT [mPFS: 11.6 vs. 11.90 months, p=0.633, hazard ratio (HR): 0.80, CI: 0.33-1.95 for pertuzumab; mPFS: 11.90 vs. 12.16 months, p=0.428, HR: 0.69, CI: 0.28-1.70 for TDM-1; mPFS: 21.10 vs. 11.90 months, p=0.25, the number of brain metastases (<5 vs. ≥5); mPFS: 11.9 vs. 12.16 months, p=0.428, HR: 0.69, CI: 0.28-1.70], the type of RT (whole brain RT vs. SRS) (p=0.575, HR: 0.83, CI: 0.43-1.58), other sites of metastasis during RT (p=0.411 HR: 0.72 CI: 0.33-1.56; p=0.772, HR: 1.10 CI: 0.54-2.24; p=0.446, HR: 1.27, CI: 0.67-2.40 for liver, lung, and bone, respectively), systemic therapy administered after RT (mPFS: 19.30 months, 95% CI: 14.77-23.82, mPFS: 11.76 months 95%, CI: 7.52-16.00, mPFS: 10.46 months, 95% CI: 6.84-14.09, p=0.081, for TDM1, trastuzumab+chemotherapy±pertuzumab, and capecitabine-lapatinib treatments, respectively). In the subgroup analysis of the 30 patients diagnosed with *de novo* metastatic breast cancer, the brain PFS was 7.23 months in patients who received breast RT and 11.76 months in patients who did not receive breast RT (p=0.098, HR: 2.14, CI: 0.86-5.30). The clinical characteristics of the patients who received and did not receive breast RT previously are presented in Table 2, which reveals that both groups had similar characteristics.

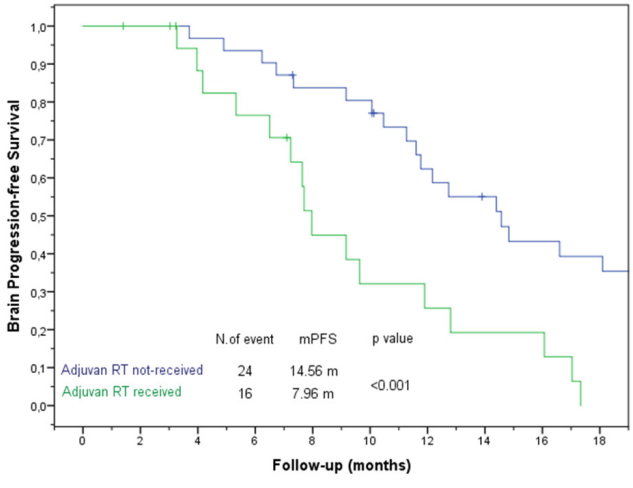

FIGURE 1: The relationship between brain PFS and whether or not breast RT was applied before.

PFS: Progression-free survival; RT: Radiotherapy

In the follow-up of patients, it was noted that 41 patients had died. The median OS time was accordingly calculated to be 25.10±4.82 months. The OS was 25.10 months for patients who did not receive adjuvant RT and 17.3 months for patients who received adjuvant RT, although the difference was not statistically significant (p=0.219).

DISCUSSION

The present study is, to the best of the author's knowledge, the first one to demonstrate that the administration of adjuvant RT diminishes the effectiveness of subsequent RT for brain metastasis.

Among all cancer types, breast cancer ranks second in terms of the development of brain metastasis, following lung cancer. The presence of brain metastasis in breast cancer patients leads to a significant reduction in the OS of patients, negatively impacting the quality of life of these patients.[10] Among the different subtypes of breast cancer, HER2-positive breast cancer is the most common subtype in which brain metastasis develops.[19] The incidence of brain metastasis is approximately 37.2% in the patients who have received multiple treatment regimens for HER2-positive breast cancer and only around 2% at the time of initial diagnosis.[15,20] Even patients with low-HER2-expression breast cancer are at an increased risk of developing brain metastasis.[21] Treatment with anti-HER2 antibodies has been demonstrated to significantly prolong the duration between the diagnosis and the development of brain metastasis. Prior to the commencement of the clinical use of trastuzumab, the duration between the diagnosis and the occurrence of brain metastasis was approximately 10 months. However, after the introduction of trastuzumab, this duration was extended to 15 months.[22] In the present study, all patients developed brain metastasis while receiving treatment with trastuzumab, and the detection occurred around 18 months after the initial diagnosis. A previous study conducted in 2011 reported achieving an iPFS of 10 months with whole-brain RT and trastuzumab treatment, while in the

TABLE 2: Baseline clinical and histological features of the patients with or without breast RT.					
			Breast RT received no (%)	Breast RT not-received no (%)	p value
Age ($\overline{X}$ ± SD)			47.35±11.60	45.00±9.68	
Time (months) from diagnosis to brain RT ($\overline{X}$ ± SD)			22.46±40.35	18.10±10.14	
Estrogen receptor expression expression		Positive	12 (60)	13 (41.9)	0.258
		Negative	8 (40)	18 (58.1)	
Stage at diagnosis		2	6 (30)	3 (9.7)	**0.020**
		3	7 (35)	5 (16.1)	
		4	7 (35)	23 (74.2)	
Prior anti-HER2 therapy	Trastuzumab	Yes	20 (100)	31 (100)	
		No	0	0	
	Pertuzumab	Yes	3 (15)	8 (25.8)	0.493
		No	17 (85)	23 (74.2)	
	TDM-1	Yes	3 (15)	4 (12.9)	1.000
		No	17 (85)	27 (87.1)	
	Lapatinib	Yes	1 (5)	1 (3.2)	1.000
		No	19 (95)	30 (96.8)	
Treatment after brain RT	Capecitabine+Lapatinib		3 (15)	6 (19.3)	0.125
	TDM-1		2 (10)	10 (32.3)	
	Trastuzumab+Cht+Pertuzumab		15 (75)	15 (48.4)	
Metastasis site (during brain RT)	Liver metastasis	Yes	5 (25)	7 (22.6)	1.000
		No	15 (75)	24 (77.4)	
	Lung metastasis	Yes	9 (45)	5 (16.1)	0.051
		No	11 (55)	26 (83.9)	
	Bone metastasis	Yes	9 (45)	17 (54.8)	0.572
		No	11 (55)	14 (45.2)	
Number of brain metastasis	Single		4 (20)	3 (9.7)	0.561
	2-5		4 (20)	8 (25.8)	
	>5		12 (20)	20 (64.5)	
RT type	Stereotactic radiosurgery		8 (40)	11 (35.5)	0.774
	Whole brain RT		12 (60)	20 (64.5)	

SD: Standard deviation; RT: Radiotherapy; Cht: Chemotherapy; HER2: Human epidermal growth factor receptor 2.

present study, this duration was approximately 12 months.[23] In an *in vivo* study on the anti-HER2-targeting treatment using Pyrotinib, it was observed that combining this treatment drug with RT significantly improved OS.[24] It was accordingly anticipated that the development of further effective anti-HER2-targeting therapies could further prolong this duration.

The susceptibility of cells to RT is influenced by the extent of DNA damage induced within the cell and the cell's capacity to activate repair mechanisms via the DNA damage response (DDR).[25] When the DDR fails to activate or the cellular DNA repair mechanisms are unable to effectively achieve DNA repair, cells enter a non-dividing state and are ultimately driven toward apoptosis via various mechanisms.[26] Cancer cells that possess an enhanced capacity for DDR tend to exhibit resistance to radiation therapy.

In head and neck cancers, for instance, the overexpression of TRIP13, which is involved in non-homologous end joining (NHEJ), and the expression of Ku80 protein reportedly promoted *in vitro* NHEJ repair and increased resistance to radiation therapy.[27,28] Activation of p53 is another critical component of the DDR mechanism, and the induction of p53 may lead to cell cycle arrest, DNA repair, or apoptosis. Clinical studies have revealed that p53 status could be a significant factor in the response to DNA-damaging agents, including RT.[29,30] Furthermore, a recent study revealed that the activation of the S100A9-RAGE-NF-κB-JunB pathway

is associated with resistance to RT in the context of brain metastasis.[18] In addition to the experimental molecular studies stated above, studies have investigated the clinical unresponsiveness to RT. Conflicting results were reported in studies comparing whole-brain RT and single high-dose RT for brain metastasis in patients with triple-negative breast cancer and lung cancer.[31-34] In the present study, no difference between WBRT and SRS was noted.

The present study identified that previous RT to the primary lesion prior to conducting RT for brain metastasis led to a significant decrease in intracranial PFS. An examination of the factors that could affect the results of the study, such as the treatments received by patients prior to and after brain RT (as presented in Table 2), and the lack of correlation between the post-RT treatments and PFS suggested that the study results are independent of the systemic treatments received.

Certain studies have suggested that the clinical course of patients diagnosed with *de novo* metastatic breast cancer is better than that of recurrent breast cancer patients.[31-34] In the present study, the proportion of *de novo* metastatic breast cancer patients was higher among the patients who did not receive breast RT, because of which a subgroup analysis had to be conducted for this subset of patients. In patients with *de novo* metastatic disease who also received breast RT, it was noted that the brain PFS was significantly shorter compared to that observed for the patients who did not receive breast RT.

Study Limitations

The limitations of the present study include its retrospective design, the fact that the molecules capable of causing RT resistance were not investigated, and the small sample size that was not sufficiently representative of the general population. In addition, the number of patients using TDM1 after RT was higher in the group that had not previously received local RT, and this could have introduced a bias in the study results and conclusions.

CONCLUSION

Breast cancer is a prevalent cause of brain metastasis, with HER2-positive brain metastasis reported as a particularly common subtype. RT is a crucial component of brain metastasis treatment. However, the present study revealed that prior RT for the primary lesion resulted in reduced efficacy of the subsequent RT for brain metastasis. This finding suggests that RT could induce molecular mutations that might contribute to the development of RT-resistant clones.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Local Research Ethics Committee of the Faculty of Medicine at Hacettepe University (date: January 24, 2023, no: GO/2308).

Informed Consent: The participants provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.C., S.A., Concept: H.Ç.Y., Ö.D., S.A., Design: H.Ç.Y., G.K., S.A., Data Collection or Processing: G.K., Y.E., Analysis or Interpretation: H.Ç.Y., D.C.G., M.G., Literature Search: M.G., F.Y., Writing: H.Ç.Y.

Conflict of Interest: Sercan Aksoy MD is editor-in-chief in Journal of Oncological Sciences. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Deniz Can Güven MD is section editor in Journal of Oncological Sciences. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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