RESEARCH ARTICLE

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Prediction of Outcomes of Brain Irradiation in Correlation with Molecular Subtypes in Patients with Metastatic Breast Cancer

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Abstract

Background: Brain metastases (BM) are a major complication in metastatic breast cancer, especially in HER2-positive and triple-negative subtypes. Despite advances in systemic therapy, BM remains associated with a poor prognosis and often requires radiotherapy. This study evaluates the outcomes of brain irradiation across subtypes and proposes a prognostic scoring system to guide treatment. **Methods:** This retrospective study analyzed data from 348 breast cancer patients with BM to develop a prognostic scoring system for radiotherapy decisions. The data included molecular subtypes, number of brain lesions, and survival outcomes. Kaplan–Meier and Cox proportional hazards models were used to identify prognostic factors. The scoring system, based on the significance of predictors, was compared with physician-selected radiotherapy techniques to assess its potential for optimizing care. **Results:** Luminal breast cancer was most prevalent (42.6%), followed by HER2-positive and triple-negative (19% each). Median BM onset was 23 months; headache was the most common symptom (48%). HER2-positive and triple-negative patients developed metastases earlier than luminal and triple-positive (P=0.001). Survival was better for luminal and triple-positive, poorer for HER2-positive and triple-negative. Patients with fewer than five brain lesions had higher survival rates (P=0.001). The scoring system incorporated molecular subtype, lesion burden, and patient characteristics. Scores above 3.5 predicted worse survival, with higher scores strongly linked to poorer outcomes (P=0.001). **Conclusion:** This study identifies key prognostic factors influencing survival in breast cancer patients with BM and proposes a scoring system to guide radiotherapy decisions. Molecular subtypes, metastatic burden, and clinical characteristics significantly affect outcomes, with HER2-positive and triple-negative subtypes showing the poorest survival. The system provides a structured approach for treatment selection, though further validation is needed to ensure its accuracy and clinical utility in personalized radiotherapy planning.

Keywords: Brain metastases metastatic- breast cancer- molecular subtypes- HER2-positive- radiotherapy outcomes

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Introduction

A considerable number of patients with metastatic breast cancer develop brain metastases (BM) along the course of the disease, particularly in human epidermal growth factor receptor 2-positive (HER2+) and triple-negative BC (TNBC) [1].

Although brain metastases are less frequent than bone and visceral metastases, they are associated with poorer prognosis and less response to systemic therapies. Recently, there is a trend toward increased incidence of brain metastases [2], this increased incidence could be due to more frequent use of sensitive diagnostic tools such as contrast-enhanced magnetic resonance imaging (MRI), increased awareness among patients and clinicians, and improved systemic therapy outcomes with subsequent prolonged survival [3].

While systemic treatments for BM have advanced, localized therapies like radiotherapy (RT) or surgery are commonly used due to systemic agents' limitations in penetrating the blood–brain barrier. Albeit tumor molecular subtypes significantly impact breast metastases particularly BM incidence and prognosis, current local treatment guidelines do not consider these subtypes [4].

When brain metastasis is diagnosed, brain irradiation is usually considered. Treatment options include conformal radiation, such as stereotactic radiotherapy, or whole brain irradiation. However, adding whole brain radiotherapy to conformal or stereotactic approaches in patients with 1–6 brain lesions has not improved overall survival (OS) and has significantly increased neurocognitive dysfunction, as demonstrated in several trials [5, 6].

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Many studies also reported higher incidence of cognitive impairment after whole-brain radiotherapy. The frequency of cognitive impairment was reported to be significantly lower among long-term survivors who had undergone conformal and stereotactic radiotherapy alone compared to whole brain. Given that brain metastasis to the hippocampus is rare and declines in cognitive functions are correlated with hippocampal irradiation, the use of intensity-modulated radiotherapy (IMRT) in whole brain radiotherapy to reduce the dose to the hippocampus (hippocampal sparing brain irradiation) has also been considered, and cognitive function is significantly preserved at six months after the completion of radiotherapy compared with that after conventional whole-brain radiotherapy [7, 8].

Previous studies have explored overall survival after brain-directed treatment based on molecular subtypes, but there's a lack of research on clinical assessment and quality of life after brain irradiation [9]. A study reported distinct recurrence patterns according to molecular subtypes, underscoring the importance of achieving local control in the HER2-positive subtype and suggesting whole-brain radiotherapy (WBRT) for triple-negative breast cancer (TNBC). However, the investigation did not evaluate whether WBRT improves clinical outcomes, particularly neurocognitive function, nor did it address the potential role of more conformal radiotherapy techniques or the impact of WBRT on overall survival [10].

This study aims to investigate the role of brain irradiation in various molecular subtypes of breast cancer, alongside other established prognostic factors. By analyzing these variables, we seek to identify the risk factors and their weight that will assist physicians in tailoring radiotherapy techniques for breast cancer patients with brain metastasis. These risk factors should be included in a scoring system intended to optimize treatment decisions, ensuring that each patient receives the most appropriate form of brain irradiation based on their individual prognostic profile.

Materials and Methods

This retrospective cohort study aimed to develop a prognostic scoring system to predict survival outcomes in breast cancer patients with brain metastasis in different molecular subgroups, guiding brain irradiation decisions. Medical records of 1243 patients from the sharing centers were reviewed for eligibility, and a total of 348 patients were included in the analysis. All patients had pathological evidence of breast cancer with radiological and/or pathological evidence of brain metastasis and were treated with either whole brain irradiation or localized irradiation of the brain metastases.

Patient selection

To reduce selection bias we reviewed consecutive medical records from participating centers during the study period and applied prespecified inclusion and exclusion criteria. Records were screened sequentially and cases meeting all eligibility criteria were included. We acknowledge that referral patterns to tertiary centers and multidisciplinary clinics may preferentially concentrate patients with symptomatic or higher burden intracranial disease; this referral bias could increase the proportion of patients with >4 lesions in our cohort compared with population based series.

Radiotherapy procedures

Radiotherapy modality, dose and fractionation were recorded from treatment charts and multidisciplinary notes. Modalities included whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS)/stereotactic radiotherapy (SRT), and focal conformal techniques (IMRT/3D CRT). Treatment choice reflected clinical judgment at the time and was therefore heterogeneous across patients and centers. We recorded the treating physician's rationale when available (lesion number, performance status, prior systemic therapy) and included modality as a covariate in adjusted analyses to mitigate confounding by indication.

Data Collection

Clinical and demographic data were collected from electronic medical records. Key variables included age, sex, molecular and pathological subtypes, stage at diagnosis, onset of brain metastasis, and presenting symptoms. Additional variables included performance status (ECOG), presence of extracranial metastases, number of brain metastases and its onset since diagnosis. Survival outcomes were recorded, with survival defined as the time from diagnosis of brain metastasis to death or last follow-up.

Statistical Analysis

Data was analyzed using SPSS version 20.0. Categorical data were represented as numbers and percentages and compared using the Chi-square test. Fisher Exact or Monte Carlo correction was applied when over 20% of cells had an expected count less than 5. Continuous data were assessed for normality with the Kolmogorov-Smirnov test. Normally distributed data were compared using the Student's t-test, while non-normally distributed data were analyzed with the Mann-Whitney test. Survival analysis was performed using the Kaplan-Meier method, with significance judged at the 5% level. Missing data were quantified for all candidate predictors. For variables with <20% missingness we used multiple imputation by chained equations (MICE) with 20 imputations; variables with ≥20% missingness were excluded from multivariable modeling. To assess robustness to residual confounding and treatment heterogeneity we performed sensitivity analyses: (a) complete case analysis, (b) models excluding patients with prior CNS directed surgery, and (c) models including radiotherapy modality and center as covariates.

Predictor Selection and model development

Predictors were selected based on clinical relevance and a thorough literature review. The initial set of predictors included age, performance status, molecular subtype, number and onset of brain metastases and presence of extracranial metastases.

A Cox proportional hazards model was used to

analyze time-to-event data. Variable selection was performed using stepwise selection, retaining predictors with a p-value < 0.05. The model was fitted using SPSS software (version 20). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC-ROC) and calibration plots. The model's discrimination and calibration were assessed to ensure accuracy and reliability.

Scoring System Development

The model coefficients were converted into a points-based scoring system. Each predictor was assigned an integer score based on its relative importance. The total score was used to stratify patients into risk categories. These categories should be guiding brain irradiation decisions (e.g., whole brain radiotherapy, localized radiotherapy) in day to day clinical practice.

The prognostic score was compared with the actual technique of radiotherapy administered based on the physician's choice to evaluate its effectiveness as a guide for selecting the appropriate radiotherapy technique. This comparison aimed to determine whether the prognostic score could reliably inform treatment decisions. It is important to note that internal and external validation of the prognostic score was not performed in this study.

Results

A total of 348 female patients were enrolled in this study. Median age was 47 years. Most of the cases had luminal subtype of BC (42.6%) while other subtypes were almost equal at about 19% each. Stage III and IV were the most common stages at diagnosis (43.2 and 42.6% respectively). The median onset of brain metastasis since diagnosis was 23 months. Headache was the most common presenting symptom (48%) while incontinence was observed in only 1.4% of cases. Most of the patients (64%) had more than 4 metastatic brain lesions (designated as "poly" in the table). Clinical improvement was observed in 79.1% of patients while radiological stationary disease was the most observed outcome (75%) (Table 1).

The onset of brain metastasis was significantly related to the molecular subtype of BC. Luminal and triple positive subtypes had longer duration till development of brain metastasis (28 and 24 months respectively). While triple negative and her2 positive cases had earlier onset of metastasis (20 and 14.5 months) (P=0.001). Meanwhile, molecular subtype did not affect the number of brain metastatic lesions neither the radiological outcome (Table 2). Kaplan Meier curve for overall survival showed better survival for luminal and triple positive subtypes (38 and 33 months). While her2 positive and triple negative had median overall survival of 19 and 22 months respectively (P=0.001) (Figure 1).

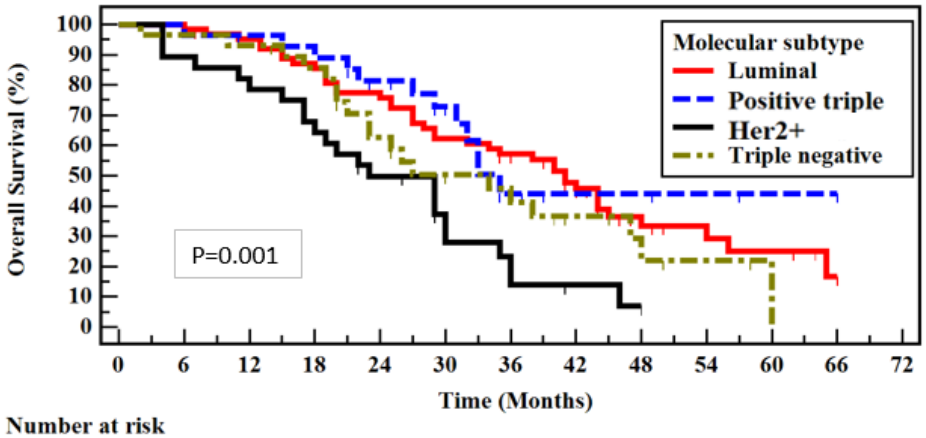
Patients who had "oligo" metastatic lesions -defined as less than 5 lesions- had higher OS compared to patient who had "poly" metastasis (42 versus 27 months, P=0.001) (Figure 2). Likewise, patients who received localized brain irradiation had better OS than those who received whole brain irradiation. This is probably due to the other interfering factors that affected survival rather than a true effect of certain technique (Figure 3).

In this study, several prognostic factors were identified as significantly influencing survival outcomes in patients with breast cancer who developed brain

Table 1. Patients and Disease Characteristics (n = 348)

	No. (%)
Age (years)	
Mean ± SD.	47.07 ± 11.37
Molecular subtype	
Luminal	148 (42.6%)
Her2+	66 (18.9%)
Triple positive	66 (18.9%)
Triple negative	68 (19.6%)
Histological subtype	
IDC	299 (85.8%)
ILC	49 (14.2%)
Stage at diagnosis	
I	5 (1.4%)
II	45 (12.8%)
III	150 (43.2%)
IV	148 (42.6%)
Onset of brain Mets	
Min. – Max.	0.0 – 60.0
Median (IQR)	23.0 (14.0 – 30.0)
Triggering symptom	
Convulsions	49 (14.2%)
Headache	167 (48.0%)
DCL	65 (18.9%)
Incontinence	5 (1.4%)
Weakness	62 (17.6%)
Number of brain Mets	
Oligo	120 (34.5%)
Poly	228 (65.5%)
Mets rather than brain	
No	113 (32.4%)
Yes	235 (67.6%)
Technique of radiation	
Localized	68 (19.6%)
WBRT	280 (80.4%)
Dose	
2000/5	232 (66.6%)
2500/5	27 (7.75%)
3000/10	89 (25.57%)
Clinical outcome	
No improvement	73 (20.9%)
Improved	275 (79.1%)
Radiological outcome	
SD	261 (75.0%)
PR	87 (25.0%)

IQR, Inter quartile range; SD, Standard deviation



Number at risk

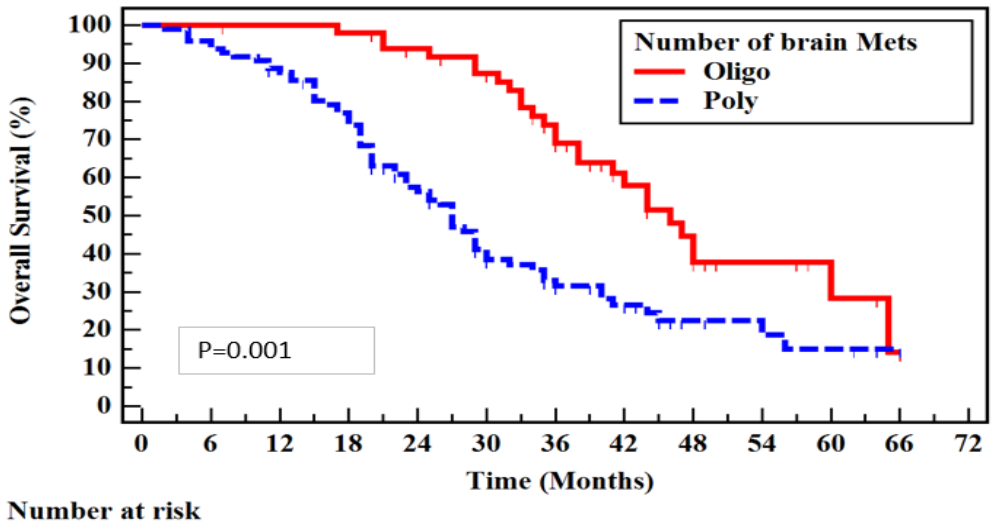
Luminal	148	98	93	84	71	59	49	33	17	11	10	0	0
Her2+	66	42	41	38	32	20	8	5	5	3	1	0	0
triple positive	66	39	34	28	20	10	5	3	0	0	0	0	0
triple negative	68	44	43	36	25	17	14	10	5	3	0	0	0

Figure 1. Kaplan-Meier Survival Curve for Overall Survival with Molecular Subtype

metastases. Younger age (<50 years) was associated with an increased risk (OR = 1.56, 95% CI: 1.30–1.87, p = 0.046). Similarly, patients with poor performance status (grade 3–4) demonstrated an elevated risk (OR = 1.52, 95% CI: 1.27–1.82, p = 0.037). Among tumor biology factors, HER2-positive status exhibited the strongest association with survival (OR = 2.97, 95% CI: 2.45–3.60, p = 0.015). Patients with triple-negative breast cancer also demonstrated a significantly increased risk (OR = 2.65, 95% CI: 2.18–3.22, p = 0.012). Regarding metastatic burden, the presence of more than four brain metastases was associated with a substantial negative impact on prognosis (OR = 1.90, 95% CI: 1.55–2.33, p = 0.003). Additionally, patients with extracranial metastases exhibited significantly lower survival rates (OR = 1.86, 95% CI: 1.52–2.28, p = 0.05). A prognostic scoring system based on these predictors was devised, with HER2-positive status contributing the highest score (2 points), followed by triple-negative subtype (1.5 points), extensive brain metastases (1 point), extracranial metastases (1 point), and patient factors such as age and performance status (0.5 points each). The weight assigned to each score was derived from the logistic regression coefficients, with fractional values rounded. This scoring approach provides a stratification model for assessing survival risk and guiding clinical decision-making (Table 3).

The ROC curve analysis for the prognostic scoring system identified a cutoff point of 3.5, at which survival was predicted to be of worse prognosis. Additionally, Kaplan-Meier survival analysis demonstrated a significant association (P=0.001) between the scoring system and overall survival, with higher scores correlating with poorer survival outcomes. (Figure 4).

Additionally, multivariate analysis was done comparing the living versus dead patients. It showed the same previous observations with triple negative and



Number at risk

Oligo	120	120	117	115	103	92	66	42	24	14	7	0	0
Poly	228	214	198	162	118	66	47	33	16	12	9	0	0

Figure 2. Kaplan-Meier Survival Curve for Overall Survival with Number of Brain Mets

Table 2. Relation between Molecular Subtype and Disease Characteristics (n = 348)

	Molecular subtype				Test of Sig.	p
	Luminal (n = 148)	Triple positive (n = 66)	Her2+ (n = 66)	Triple negative (n = 68)		
Onset of brain Mets						
Min. – Max.	0 – 60	0 – 55	0 – 42	1 – 54	H=17.527*	0.001*
Median (IQR)	28 (16.50 –36.50)	24 (17.50 – 25)	14.50 (7 – 22.50)	20 (15 – 26)		
Number of brain Mets						
Oligo	44 (30.2%)	31 (47%)	19 (28.6%)	26 (38.3%)	χ^2= 2.877	0.411
Poly	104 (69.8%)	35 (53%)	47 (71.4%)	42 (61.7%)		
Radiological outcome						
SD	118 (79.1%)	45 (68.1%)	54 (81.8%)	45 (66.2%)	χ^2= 3.555	0.314
PR	31 (20.9%)	21 (31.8%)	12 (18.1%)	23 (33.8%)		

IQR, Inter quartile range; SD, Standard deviation; χ^2, Chi square test; H, H for Kruskal Wallis test; p, p value for Relation between Molecular subtype and outcomes; *, Statistically significant at $p \leq 0.05$

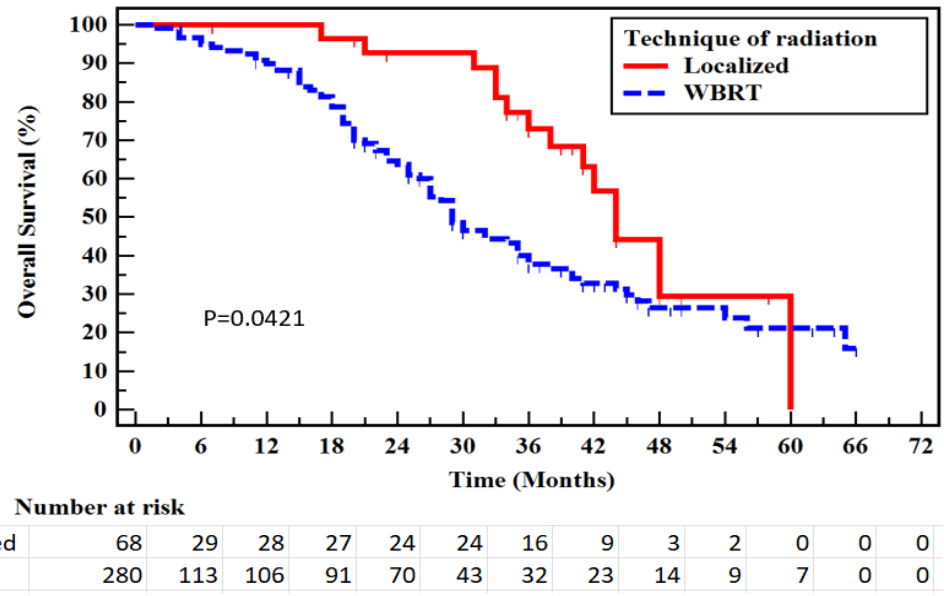


Figure 3. Kaplan-Meier Survival Curve for Overall Survival with Technique of Radiation

her2 positive being the worst subtypes of breast cancer with brain metastasis (P=0.009 and 0.004 respectively). Interestingly, patients who presented with muscle weakness e.g. paraplegia had poorer outcomes compared to other forms of clinical presentation (Table 4).

Sensitivity analyses produced effect estimates consistent with the primary analysis: complete case models and models additionally adjusting for radiotherapy modality and treating center yielded similar hazard ratios for the main predictors, supporting the robustness of our findings despite treatment heterogeneity.

Discussion

Our study presents a retrospective analysis of a cohort of 348 female patients with breast cancer who developed brain metastases (BCBM) and were treated with brain irradiation. The primary aims were to characterize this

Table 3. The Suggested Predictive Scoring System Based on Binary Logistic Regression

Predictor	Coefficient (β)	Odds ratio	p-value	95% confidence interval	Prognostic score (rounded)
Age below 50	0.25	1.56	0.046	(1.30, 1.87)	0.5
Performance 3,4	0.45	1.52	0.037	(1.27, 1.82)	0.5
Her2 +	0.71	2.97	0.015	(2.45, 3.60)	2
Triple negative	0.55	2.65	0.012	(2.18, 3.22)	1.5
More than 4 mets	0.9	1.9	0.003	(1.55, 2.33)	1
Extracranial mets	0.34	1.86	0.05	(1.52, 2.28)	1

Table 4. Multivariate COX Regression Analysis for the Parameters Affecting Overall Survival (n = 221 vs. 127)

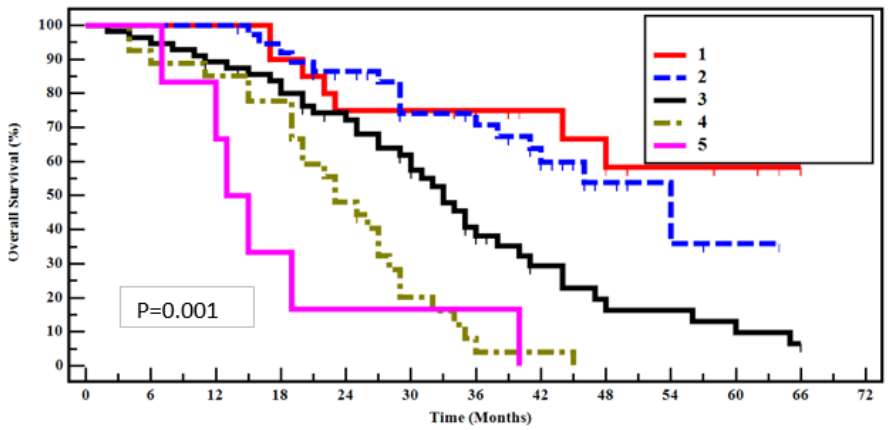
	p	#Multivariate HR (LL – UL 95%C.I)
Molecular subtype		
Lumina®		1
Triple positive	0.405	0.744 (0.371 – 1.492)
Triple negative	0.009	2.704 (1.280 – 5.711)
Her2+	0.004*	1.455 (0.677 – 3.127)
Triggering symptom		
Headache®		1
Convulsions	0.811	1.086 (0.554 – 2.129)
DCL	0.625	0.850 (0.444 – 1.629)
Incontinence	0.08	3.879 (0.851 – 17.676)
Weakness	0.036*	1.872 (1.042 – 3.366)
Number of brain Mets		
Oligo ®		1
Poly	0.006*	2.630 (1.315 – 5.260)
Technique of radiation		
Localized ®		1
WBRT	0.065	1.172 (0.041 – 1.715)
Dose		
2000/5	0.106	3.744 (0.755 – 18.572)
2500/5	0.426	0.568 (0.141 – 2.290)
3000/10	0.162	2.995 (0.645 – 13.912)
5000/5 ®		1
Prognostic score	<0.001*	2.158 (1.643 – 2.835)
Radiological outcome		
SD	0.181	1.553 (0.815 – 2.959)
PR ®		1

HR, Hazard ratio; C.I, Confidence interval; #, All variables with p<0.05 was included in the multivariate; LL, Lower limit; *, Statistically significant at p ≤ 0.05; UL, Upper Limit

patient population, assess outcomes following irradiation, and develop a prognostic scoring system to predict survival and inform the choice between whole brain irradiation (WBRT) and localized irradiation.

The demographic and clinicopathological characteristics of our cohort provide important context. We observed that luminal subtypes constituted the largest proportion (42.6%) of patients presenting with BCBM for irradiation treatment, followed by triple-negative (TN) and HER2-positive subtypes, which were represented in nearly equal proportions (approximately 19% each). This distribution, while representing the prevalence of subtypes within our treated BCBM population, warrants comparison with literature describing the incidence risk of developing brain metastases among different breast cancer subtypes. The sources consistently indicate that HER2-positive and TN subtypes carry a significantly higher risk and incidence of developing brain metastases compared to the HR-positive/HER2-negative (luminal) subtype. For instance, a meta-analysis reported pooled cumulative incidences of 31% for HER2+ and 32% for TN subgroups with metastatic breast cancer, versus only 15% for HR+/HER2− MBC [11]. Another large real-world database (ESME MBC) confirmed the increased risk for HER2-positive and HR-negative tumors but noted that the majority of patients with CNS metastases in their cohort actually had HER2−/HR+ tumors (45.3%), likely reflecting the higher overall incidence of this subtype in the broader MBC population [12, 13]. Our finding that luminal is the most frequent subtype in our treated cohort, despite TN and HER2+ having a higher propensity for BM, could be influenced by factors such as the overall prevalence of subtypes in the general breast cancer population, potential differences in overall survival allowing luminal patients more time to develop BM, or referral patterns to our institution.

The median time from initial breast cancer diagnosis to the development of brain metastasis in our study was 23 months. This finding aligns with the kinetics of BM



No. at risk													
Score 1	47	47	47	42	35	33	26	21	14	9	7	0	0
Score 2	92	92	89	80	71	54	49	31	14	5	2	0	0
Score 3	132	125	115	101	82	56	33	21	12	12	7	0	0
Score 4	63	56	54	49	31	12	2	2	0	0	0	0	0
Score 5	14	14	9	5	2	2	2	0	0	0	0	0	0

Figure 4. Kaplan-Meier Survival Curve for Overall Survival with the Predictive Score

development reported in the literature, particularly for aggressive subtypes. Studies have demonstrated that the time to BM development is significantly shorter in HER-2 overexpressing and triple-negative subtypes than in luminal subtypes. Specific median times reported include 22.8-27 months for TNBC and 16.8-30 months for HER2 positive. Given the substantial representation of TN and HER2+ subtypes in our cohort, an overall median time of 23 months is broadly consistent with these faster kinetics, though it may be shorter than the median times reported for luminal subtypes (e.g., 33.5-40.6 months) [14, 15].

Symptoms at presentation in our cohort were typical, with headache being the most common symptom (48%). Furthermore, a significant proportion of our patients (64%) presented with more than 4 metastatic brain lesions. This is a notable characteristic of our study population, as the number of brain metastases is a critical factor influencing prognosis and treatment decisions. While the literature often categorizes patients by lesion number (e.g., 1-3 vs. >3), the high prevalence of patients with >4 lesions suggests our cohort may include a higher proportion of individuals with more diffuse or advanced intracranial disease compared to some studies focusing on patients primarily amenable to stereotactic radiosurgery (SRS), which is typically favored for a limited number of lesions (<4) [16, 17].

Regarding treatment outcomes following brain irradiation, our study reported clinical improvement in 79.1% and radiological stationary disease in 75% of patients. These metrics indicate a favorable response to local therapy in a substantial proportion of patients. Direct quantitative comparison of these outcomes to the provided literature is challenging, as the primary endpoints reported in the sources for irradiation effectiveness are typically overall survival (OS) and distant intracranial control (DIC). The prognosis of patients with BCBM remains poor overall, with reported median OS times after BM diagnosis varying significantly by subtype and treatment received. For example, median OS after CNS metastasis diagnosis was reported as 7.9 months in a large cohort, while a study on SRT patients reported 2-year OS rates ranging from 12% (TN) to 54% (HR+/HER2+). Our findings on clinical and radiological response highlight the immediate impact of irradiation on symptoms and disease stability, which are important intermediate outcomes [18, 19].

A central component of our study was the development of a prognostic scoring system intended to predict survival and guide the choice between WBRT and localized irradiation. The importance of identifying prognostic factors to personalize treatment in BCBM is well-established in the literature. Factors such as molecular subtype, performance status, number of brain lesions, and presence of extracranial disease are known predictors of survival and are incorporated into existing validated prognostic indices like the Graded Prognostic Assessment (GPA) and the modified breast-GPA. The modified breast-GPA, which includes molecular subtype, has been validated for its ability to predict both overall survival and distant intracranial control. Our effort to create a new score specifically aimed at guiding the selection of irradiation modality represents a clinically relevant objective, as the optimal local treatment strategy in the context of differing lesion burden and subtype is an area of ongoing research [19, 20].

However, a significant limitation of our study is the lack of internal and external validation for the developed prognostic score. Validation in independent patient cohorts is a critical step in confirming the reliability and generalizability of any prognostic model. Without validation, our score remains exploratory and is not ready for widespread clinical application. Existing validated scores provide a benchmark for predicting survival in BCBM. Future work should focus on validating our proposed scoring system to determine its accuracy and clinical utility, particularly its ability to differentiate prognosis and predict differential benefit from WBRT versus localized irradiation.

Our study has several limitations inherent to its retrospective design that warrant careful consideration. First, selection and referral bias may have influenced cohort composition. Although we reviewed consecutive records and applied prespecified eligibility criteria, participating tertiary and referral centers may receive a disproportionate number of patients with symptomatic or more extensive intracranial disease; this likely contributed to the high proportion of patients with >4 lesions in our series and may limit direct comparability with population based cohorts or SRS focused series. Second, incomplete or missing data are an unavoidable challenge in retrospective chart reviews. We quantified missingness for all candidate predictors and used multiple imputation for variables with low to moderate missingness; variables with high missingness were excluded from multivariable modeling. Sensitivity analyses (complete case and models adjusted for radiotherapy modality and center) produced similar effect estimates, but residual bias from unmeasured or incompletely recorded variables remains possible.

Third, treatment heterogeneity is an important limitation. Radiotherapy modality, dose fractionation, and concurrent or prior systemic therapies varied across patients and centers because treatment decisions were individualized and evolved over the study period. Although we adjusted for key prognostic factors and included modality and center in sensitivity models, confounding by indication cannot be fully excluded; patients selected for localized techniques generally had fewer lesions and better performance status, which may explain some of the unadjusted survival differences observed between techniques. Finally, receptor conversion between primary tumor and brain metastasis and the absence of systematic neurocognitive and quality of life assessments limit our ability to draw conclusions about biologic mechanisms and functional outcomes. These limitations underscore the need for prospective studies and external validation of our prognostic score before clinical implementation.

The proposed prognostic score incorporates the variables outlined in Table 3, derived from expected patient survival and the optimal cutoff determined through receiver operating characteristic (ROC) curve analysis.

Patients with a score exceeding 3.5 are advised to undergo whole-brain irradiation, whereas those scoring below this threshold may be considered candidates for localized irradiation techniques, tailored to disease burden and clinical presentation.

In conclusion, our study provides data on a large cohort of BCBM patients treated with irradiation, highlighting characteristics such as the prevalence of luminal subtypes in this treated population, the median time to BM onset consistent with aggressive disease kinetics, and the high burden of intracranial disease (>4 lesions) in a majority of patients. We have developed a novel prognostic score with the potential to guide irradiation strategy, which is easy and simple to use despite lacking validation. Future research should focus on validating prognostic models in independent cohorts and integrating biological insights, such as those related to homologous recombination deficiency (HRD) and the brain microenvironment, to further personalize the management of breast cancer brain metastases.

The observed prevalence of luminal subtype (42.6%) among patients who received brain irradiation in our series requires careful interpretation. Several non mutually exclusive mechanisms can explain this finding. First, survival bias: patients with hormone receptor positive disease often experience longer systemic disease control and overall survival, thereby increasing the time window during which symptomatic CNS disease can emerge and be referred for local therapy [13]. Second, referral and center bias: tertiary referral centers and multidisciplinary clinics tend to receive patients with symptomatic or more advanced intracranial disease, which can enrich treated cohorts for subtypes that survive longer or for patients who develop late CNS events [21]. Third, differences in imaging and detection practices: cohorts that rely on symptom driven imaging will preferentially capture symptomatic lesions, whereas programs with routine MRI surveillance detect asymptomatic CNS disease earlier and may show a different subtype mix; variability in surveillance policies therefore alters the case mix [22]. Fourth, receptor conversion and intratumoral evolution: discordance between receptor status in the primary tumor and paired brain metastases is well documented; if metastatic tissue is not re biopsied, subtype misclassification can occur and alter apparent subtype frequencies (5–25% discordance reported) [23]. Fifth, treatment selection and competing systemic risks: systemic therapies with differing CNS penetration and efficacy create competing risks—some regimens control extracranial disease but not CNS micrometastases, influencing which patients survive to present with brain metastases and receive irradiation [24]

In conclusion, this study identifies key prognostic factors influencing survival in breast cancer patients with brain metastases and proposes a scoring system to guide irradiation decisions. Molecular subtypes, metastatic burden, and clinical characteristics significantly impact outcomes, with HER2-positive and triple-negative subtypes showing the poorest survival. While the scoring system offers a structured approach to treatment selection, further validation is essential to ensure its accuracy and clinical utility in personalized radiotherapy planning.

Author Contribution Statement

Each author participated equally in the conception, execution, and reporting of this study.

Acknowledgements

Ethical Approval and Consent to Participate: This study was subject to ethical approval by Menoufia University, faculty of medicine ethical committee and in concordance with the declaration of Helsinki. Approval number 7/2024-ONCO. No consent was requested from patients as it is a retrospective study.

Consent for publication

All authors approved the final version of the manuscript.

Use of large language models

Artificial intelligence (AI) model has been used for rephrasing and English proofreading of this manuscript as all authors are non-English native speakers. No generative AI has been used in this manuscript.

Conflicts of interest

all authors declare no conflict of interest.

Abbreviations

3DCRT: conformal radiotherapy
BM: Brain metastases
IDC: invasive ductal carcinoma
ILC: invasive lobular carcinoma
IMRT: intensity-modulated radiotherapy
MRI: magnetic resonance imaging
OS: overall survival
PR: partial response
QOL: quality of life
RT: radiotherapy
HRD: homologous recombination deficiency
SD: stable disease
TNBC: triple-negative breast cancer
WBRT: Whole Brain Radiotherapy

References

1. Witzel I, Oliveira-Ferrer L, Pantel K, Müller V, Wikman H. Breast cancer brain metastases: Biology and new clinical perspectives. Breast Cancer Res. 2016;18(1):8. https://doi.org/10.1186/s13058-015-0665-1.
2. Brufsky AM, Mayer M, Rugo HS, Kaufman PA, Tan-Chiu E, Tripathy D, et al. Central nervous system metastases in patients with her2-positive metastatic breast cancer: Incidence, treatment, and survival in patients from registher. Clin Cancer Res. 2011;17(14):4834-43. https://doi.org/10.1158/1078-0432.Ccr-10-2962.
3. Pestalozzi BC, Holmes E, de Azambuja E, Metzger-Filho O, Hogge L, Scullion M, et al. Cns relapses in patients with her2-positive early breast cancer who have and have not received adjuvant trastuzumab: A retrospective substudy of the hera trial (big 1-01). Lancet Oncol. 2013;14(3):244-8. https://doi.org/10.1016/s1470-2045(13)70017-2.
4. Kim JS, Kim K, Jung W, Shin KH, Im SA, Kim HJ, et al. New

brain metastases after whole-brain radiotherapy of initial brain metastases in breast cancer patients: The significance of molecular subtypes (krog 16-12). Breast Cancer Res Treat. 2021;186(2):453-62. https://doi.org/10.1007/s10549-020-06043-0.
5. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A european organisation for research and treatment of cancer phase iii trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: Quality-of-life results. J Clin Oncol. 2013;31(1):65-72. https://doi.org/10.1200/jco.2011.41.0639.
6. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: Individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2015;91(4):710-7. https://doi.org/10.1016/j.ijrobp.2014.10.024.
7. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (rtog 0933): A phase ii multi-institutional trial. J Clin Oncol. 2014;32(34):3810-6. https://doi.org/10.1200/jco.2014.57.2909.
8. Harth S, Abo-Madyan Y, Zheng L, Siebenlist K, Herskind C, Wenz F, et al. Estimation of intracranial failure risk following hippocampal-sparing whole brain radiotherapy. Radiother Oncol. 2013;109(1):152-8. https://doi.org/10.1016/j.radonc.2013.09.009.
9. Jeon W, Jang BS, Jeon SH, Kim JH, Kim YJ, Kim SH, et al. Analysis of survival outcomes based on molecular subtypes in breast cancer brain metastases: A single institutional cohort. Breast J. 2018;24(6):920-6. https://doi.org/10.1111/tbj.13111.
10. Cagney DN, Lamba N, Montoya S, Li P, Besse L, Martin AM, et al. Breast cancer subtype and intracranial recurrence patterns after brain-directed radiation for brain metastases. Breast Cancer Res Treat. 2019;176(1):171-9. https://doi.org/10.1007/s10549-019-05236-6.
11. Kuksis M, Gao Y, Tran W, Hoey C, Kiss A, Komorowski AS, et al. The incidence of brain metastases among patients with metastatic breast cancer: A systematic review and meta-analysis. Neuro Oncol. 2021;23(6):894-904. https://doi.org/10.1093/neuonc/noaa285.
12. Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer. 2019;121(12):991-1000. https://doi.org/10.1038/s41416-019-0619-y.
13. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010;28(20):3271-7. https://doi.org/10.1200/jco.2009.25.9820.
14. Sperduto PW, Kased N, Roberge D, Chao ST, Shanley R, Luo X, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol. 2013;112(3):467-72. https://doi.org/10.1007/s11060-013-1083-9.
15. Hulsbergen AFC, Lamba N, Claes A, Kavouridis VK, Lin NU, Smith TR, et al. Prognostic value of brain metastasis-free interval in patients with breast cancer brain metastases. World Neurosurg. 2019;128:e157-e64. https://doi.org/10.1016/j.wneu.2019.04.072.
16. Mills MN, Thawani C, Figura NB, Oliver DE, Soyano AE, Etame A, et al. Breast cancer subtype predicts clinical outcomes after stereotactic radiation for brain metastases. J Neurooncol. 2021;152(3):591-601. https://doi.org/10.1007/s11060-021-03735-5.
17. Simsek M, Aliyev A, Baydas T, Besiroglu M, Demir T, Shbair AT, et al. Breast cancer patients with brain metastases: A cross-sectional study. Breast J. 2022;2022:5763810. https://doi.org/10.1155/2022/5763810.
18. Pasquier D, Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, et al. Treatment and outcomes in patients with central nervous system metastases from breast cancer in the real-life esme mbc cohort. Eur J Cancer. 2020;125:22-30. https://doi.org/10.1016/j.ejca.2019.11.001.
19. Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, et al. Beyond an updated graded prognostic assessment (breast gpa): A prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys. 2020;107(2):334-43. https://doi.org/10.1016/j.ijrobp.2020.01.051.
20. Griguolo G, Jacot W, Kantelhardt E, Dieci MV, Bourgier C, Thomssen C, et al. External validation of modified breast graded prognostic assessment for breast cancer patients with brain metastases: A multicentric european experience. Breast. 2018;37:36-41. https://doi.org/10.1016/j.breast.2017.10.006.
21. Bailleux C, Eberst L, Bachelot T. Treatment strategies for breast cancer brain metastases. British journal of cancer. 2021 Jan 5;124(1):142-55. doi:10.1038/s41416 020 01175 y.
22. Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. Cns metastases in breast cancer: Old challenge, new frontiers. Clin Cancer Res. 2013;19(23):6404-18. https://doi.org/10.1158/1078-0432.Ccr-13-0790.
23. Schrijver W, Suijkerbuijk KPM, van Gils CH, van der Wall E, Moelans CB, van Diest PJ. Receptor conversion in distant breast cancer metastases: A systematic review and meta-analysis. J Natl Cancer Inst. 2018;110(6):568-80. https://doi.org/10.1093/jnci/djx273.
24. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for her2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597-609. https://doi.org/10.1056/NEJMoa1914609.