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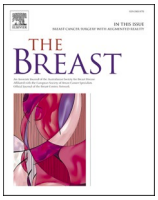

Comprehensive analysis of stereotactic Radiosurgery outcomes in triple-negative breast cancer patients with brain metastases: The influence of immunotherapy and prognostic factors☆

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ABSTRACT

Introduction: Breast cancer stands as the second most common solid tumors with a propensity for brain metastasis. Among metastatic breast cancer cases, the brain metastasis incidence ranges from 10 % to 30 %, with triple-negative breast cancer (TNBC) displaying a heightened risk and poorer prognosis. SRS has emerged as an effective local treatment modality for brain metastases; however, data on its outcomes specifically in pure triple-negative subtype remain scarce.

Method: We retrospectively reviewed the electronic medical records of all brain metastasis (BM) TNBC patients treated with SRS. Patient, tumour characteristics and treatment details data were collected. This retrospective cohort study aimed to evaluate local control (LC), distant brain metastasis free survival (DBMFS), and overall survival (OS) outcomes in TNBC patients undergoing SRS for brain metastases while identifying potential prognostic factors.

Result: Forty-three patients with TNBC and brain metastases treated with SRS between January 2017 and 2023 were included. The study found rates of LC (99 % at 1 year) and DBMFS (76 % at 1 year) after SRS, with brain metastasis count (p = 0,003) and systemic treatment modality (p = 0,001) being significant predictors of DBMFS. The median OS following SRS was 19.5 months, with neurological deficit (p = 0.003) and systemic treatment modality (p = 0.019) identified as significant predictors of OS.

Conclusion: SRS demonstrates favourable outcomes in terms of local control and distant brain metastasis-free survival in TNBC. Neurological deficit and systemic treatment significantly influence overall survival, emphasizing the importance of personalized treatment approaches and (magnetic resonance imaging) MRI surveillance based on these factors.

1. Introduction

Breast cancer ranks as the second most prevalent solid tumor with a propensity for metastasis to the brain [1,2]. Within the realm of metastatic breast cancer, the incidence of brain metastasis ranges from 10 % to 30 % [3]. Notably, triple-negative breast cancer (TNBC) carries an elevated risk of developing brain metastases and is associated with a less favourable prognosis compared to other subtypes [4].

Advancements in systemic treatments for metastatic breast cancer have significantly extended overall survival. However, while the control of extra-cranial disease has improved and survival times have lengthened, this has paradoxically led to an increased risk of developing brain metastases [5,6]. Nonetheless, the effectiveness of systemic treatment drugs in penetrating the central nervous system (CNS) remains limited. Moreover, the lack of adequate representation of patients with brain metastases in many studies, often due to their exclusion, impedes a thorough understanding of this particular patient subgroup [7,8].

Stereotactic Radiosurgery has been a reliable and highly effective

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modality for the local treatment of brain metastases for many years [3]. Although TNBC exhibits a distinct behavioural pattern compared to other types of breast cancer, there is a scarcity of data in the literature specifically addressing the outcomes of SRS in pure triple-negative sub-type. Hence, the objective of this study is to evaluate local control (LC), distant brain metastasis free survival (DBMFS), and overall survival (OS), as well as to identify potential prognostic factors associated with CNS progression and OS in patients treated with SRS for brain metastases in the setting of triple-negative breast cancer.

2. Methods

We conducted an Institutional Review Board IRB-approved (ASM-EK-21/161) retrospective cohort study, encompassing all breast cancer patients with brain metastases treated with SRS. All procedures were performed in compliance with relevant laws and institutional guidelines. Informed consent was obtained from all patients. The medical records were retrospectively reviewed. The study comprised patients diagnosed with triple-negative breast cancer based on biopsy or post-surgical pathology following the primary breast cancer. Brain metastasis diagnosis relied on imaging findings and/or biopsy. The study cohort included all patients with prior BM surgery and excluded those with prior Whole brain radiotherapy (WBRT). Patients from two tertiary centers were included, and data were collected from January 2017 to January 2023.

Two different radiation platforms, the robotic CyberKnife® (Accuray Incorporated, Sunnyvale, CA) and Varian linac-based system (Varian Medical Systems, Palo Alto, CA), were utilized for SRS delivery. The choice of 1, 3, or 5 fractions depended on the tumor volume, following the physician's policy. Patients receiving a daily fraction dose $\geq$6 Gy in $\leq$5 fractions were included.

Treatments were planned based on T1 contrast enhanced (magnetic resonance imaging) MRI. Generally, dosing adhered to the results from the Radiation Therapy Oncology Group 90-05 dose escalation trial.

After SRS, patients underwent follow-up with clinical and radiographic surveillance according to institutional standards. Patients were followed up with brain MRIs at 3 months after SRS and subsequently every 3 months thereafter, or earlier if neurological deficits occur. Our extracranial imaging protocols predominantly rely on PET-CT, thoracoabdominal CT, or abdominal MR every 3 months. 88.3 % of the patients were followed up in accordance with these protocols.

Data collection encompassed age, number of brain metastases, lesion locations in the brain, dose-fractions, treatment date, extracranial disease status, prior brain metastasis surgery, neurological deficits (motor or sensory loss, vision, hearing, swallowing, balance problems, etc.), systemic treatment, salvage WBRT, time until the first CNS progression after SRS, and the type of first CNS progression (local, distant, leptomeningeal).

Systemic therapy was classified as chemotherapy and immunotherapy which is delivered within 4 weeks either before or after SRS. All local recurrences and radiation necrosis using contrast-enhanced MRI and additional perfusion MRI according to the response assessment in neuro-oncology (RANO) criteria [9]. Development of new brain metastasis outside the prior SRS treatment volume was considered distant brain metastasis. Leptomeningeal failure was determined by MRI evidence of new nodular enhancement of the dura, diffuse leptomeningeal enhancement, or positive cerebrospinal fluid cytology.

3. Statistics

Descriptive statistics were utilized to summarize the patient and treatment characteristics of the cohort. The clinical outcomes, including LC, DBMFS, and OS, were estimated with the Kaplan–Meier (KM) method with the log-rank test used to assess differences between groups. Cox regression (univariate-multivariate) was used for survival analysis. Local control, DBMFS is calculated per patient. Overall survival was defined as the time from SRS to death or last follow up. The follow-up period was calculated from the completion of SRS to the last follow-up or until death.

SPSS 27.0 (IBM SPSS Inc.) program was used in the analysis.

4. Results

Between January 2017 and January 2023, 43 patients and 129 lesions were included in the study, with an average follow-up period of 16 months (95 % CI 12–20 months). The median age was 50 (range: 28–71). The median of maximum tumor diameter was 14.5 mm (IQR 11,5–26). The prescription doses were 18–21 Gy in a single fraction, 21–27 Gy in three fractions and 25–30 Gy in five fractions. Patient, tumor and treatment characteristics are summarised in Table 1. The

Table 1
Patient, tumor and treatment characteristics.

BM Number	Number (%)
Median	2
Range	1–10
IQR	1–4
BM Number	
1–3	2 9 [4,67]
>3	14 [6,32]
Maximum Tumor Diameter	
Median	14,5
Range	2–46
IQR	11,5-26
Time from BC to BM diagnosis	
Median	29,6
Range	0-81,7
IQR	14,1–43,7
BM Presentation	
Synchronous	5 [6,11]
Metachronous	38 [4,88]
Neurological Deficit	
Absent	9 [10]
Present	33 [7,76]
Unknown	1 [2,3]
Extracranial Metastasis	
Absent	12 [9,27]
Present	30 [8,69]
Unknown	1 [2,3]
Type of Systemic Treatment	
Chemotherapy Regimen	24 [8,55]
Capacitabine	5 [6,11]
Gemcitabine + Cisplatin	3 [7]
Paclitaxel	3 [7]
Gemcitabine + Carboplatin	2 [4,6]
Gemcitabine	1 [2,3]
Carboplatin + Paclitaxel	1 [2,3]
Eribulin	1 [2,3]
Cisplatin + Etoposide	1 [2,3]
Everolimus	1 [2,3]
Unknown	6 [11]
Immunotherapy	19 [2,44]
Pembrolizumab	17 [6,39]
Nivolumab	2 [4,6]
Surgical resection prior to SRS	
Yes	11 [6,25]
No	32 [4,74]
SRS platform	
Robotic	39 [7, 90]
Linac-based	4 [3,9]
Fraction Number	
1	6 [11]
3	34 (79)
5	3 [7]
GPA score	
1	6 [11]
2	24 [8,55]
3	13 [2,30]

IQR interquartile range, BC breast cancer, BM brain metastasis, GPA Graded Prognostic Assessment.

demographic, clinical, and treatment parameters of patients receiving chemotherapy and immunotherapy showed no statistically significant differences (see Supplementary Table).

Ten patients experienced local recurrence with a median time to recurrence of 17.9 months (range: 8.2–37.7). Local control rates were 98 % at 1 year and 85 % at 2 years per patient (Fig. 1a) and 99 % at 1 year and 95 % at 2 years per lesion (Fig. 1b). The maximum tumor diameter ($p = 0.047$) and prior surgery ($p = 0.01$) were only clinical variables with local recurrence. The local control rates per lesion were 99 % vs. 97 % at 1 year and 97 % vs. 87 % at 2 years for the chemotherapy and immunotherapy groups, respectively ($p = 0.826$).

Twenty-three patients developed distant brain metastases, with an average time of 10 months (range: 1–72). Distant brain metastasis-free survival rates were 76 % at 1 year and 45 % at 2 years (Fig. 1c). Cox regression analysis revealed 1–3 vs > 3 brain metastasis ($p = 0.003$) and used systemic treatment chemotherapy vs immunotherapy ($p = 0.001$) as significant predictors of DBMFS (Fig. 2a–b). The DBMFS rates were 54 % vs. 87 % at 1 years, 12 % vs. 59 % for chemotherapy and immunotherapy groups at 2 years, respectively.

Salvage WBRT was administered to 12 patients, with a median time of 17 months post-SRS. WBRT-free survival rates were 93 % at 1 year and 78 % at 2 years. Leptomeningeal disease occurred in 3 patients at 8-, 28- and 30-months post-SRS, while 2 patients developed radionecrosis.

The median OS after SRS was 19.5 months (95 % CI). Overall survival rates were 64 % at 1 year and 35 % at 2 years (Fig. 1d). Neurological deficit ($p = 0.003$) and systemic treatment chemotherapy vs immunotherapy ($p = 0.019$) were only clinical variables associated with OS (Fig. 3). The 1-year survival rates were 51 % vs. 77 %, and 10 % vs. 41 % at 2 years for patients with and without neurological deficits, respectively.

5. Discussion

In our current analysis, we observed notably extended disease-free survival rates among brain metastatic TNBC patients treated with SRS, particularly in those with 1–3 metastases compared to those with >3 metastases. Moreover, patients receiving immunotherapy demonstrated significantly prolonged DFS compared to those receiving chemotherapy. This study marks the first instance in the literature showcasing the intracranial efficacy of immunotherapy in breast cancer brain metastases. Furthermore, our findings revealed significantly enhanced overall survival rates in patients devoid of neurological deficits relative to those with deficits, as well as in patients undergoing immunotherapy versus chemotherapy.

Routine brain MRI is not recommended in breast cancer staging [12]. The high rate of patients presenting with neurological deficits in this study also supports the fact that only symptomatic patients are imaged with brain MRI [13,14]. Additionally, better survival results in asymptomatic patients have been in accordance with current literature [13,14]. This underscores the importance of routine brain MRI staging, especially in high-risk subtypes, in metastatic diseases.

In the literature, the average survival after SRS in brain metastatic TNBC has been reported as 8.5–14.8 months [11,15–17]. Brain metastases represent a significant source of mortality and morbidity [18]. Consequently, controlling them is crucial. Although the detection rate of brain metastasis is low in the primary staging, it exceeds 30 % in certain metastatic breast cancer subtypes, such as HER2-positive and triple-negative [19]. Randomized trials have demonstrated that overall survival outcomes are comparable between SRS and WBRT, with an increased risk of distant brain recurrence in SRS applications. Conversely, WBRT has been linked to cognitive decline [10,20,21]. Studies reported local control rates after SRS ranging from 67 % to 72.5 % and distant brain control 45 % to 73 % at 1 year across various primary tumors with brain metastases [10,20,21]. In our series, comparable distant brain control rates of 76 % and superior local control rates of 98 % following SRS can be achieved in triple-negative breast cancers with 1–10 brain metastases. Local control is influenced by a multitude of variables, encompassing dosage, total dose fractionation, and the number of fractions, along with the volume of metastasis and primary histology [22]. Furthermore, the application of systemic therapies may exert potential effects on these factors. A study involving individuals diagnosed with lung cancer and melanoma brain metastasis, treated with SRS, revealed that dual immunotherapy was associated with improved local control rates [23]. Additionally, despite variations in clinician decisions regarding WBRT, 78 % of patients in our series did not undergo WBRT within 2 years. Particularly in the realm of immunotherapy, protection against distant brain metastases seems to persist in the long term with 2-year DBMFS rates between immunotherapy and

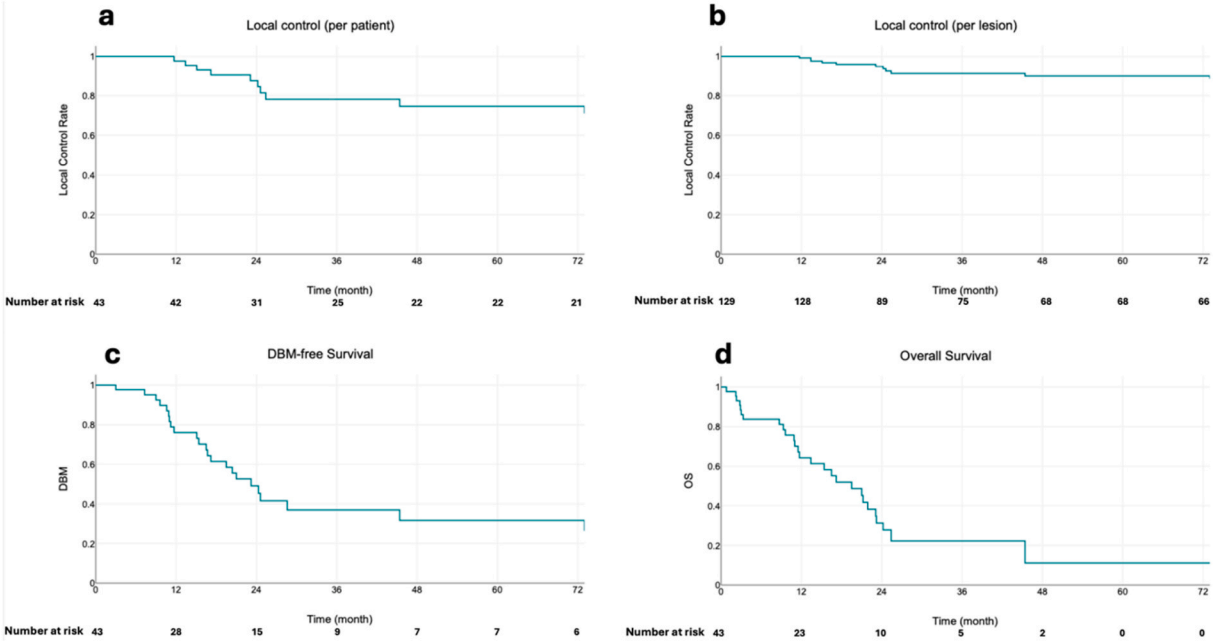

Fig. 1. Kaplan–Meier curves depicting **a** local control (per patient), **b** local control (per lesion) **c** distant brain control, **d** overall survival from the date ofstereotactic radiation.

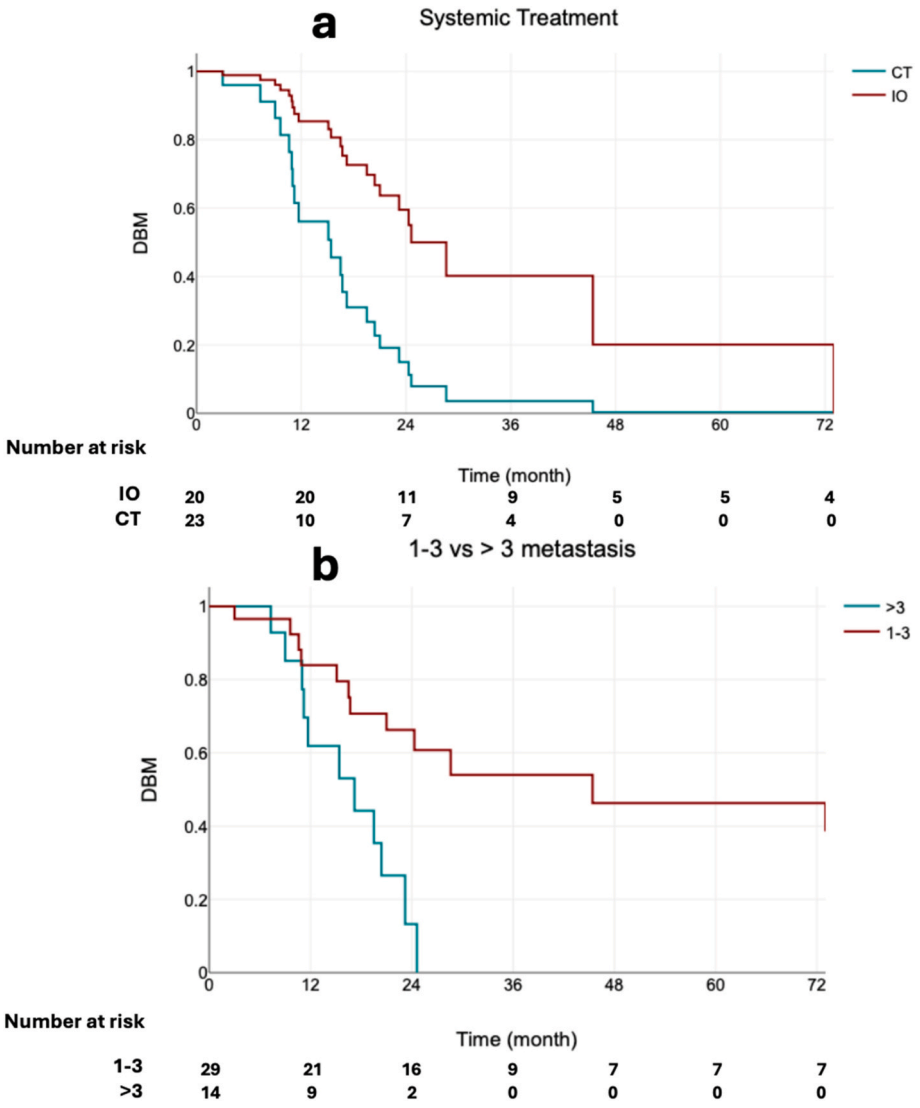

Fig. 2. Distant brain metastasis free survival by systemic treatment type (a) and brain metastasis count (b).

chemotherapy were 55 % versus 11.2 %, respectively. Long-term protection against distant brain metastases, particularly in the context of immunotherapy, supports the safe preference for SRS over WBRT, especially in patients with limited metastases who will receive immunotherapy. According to our study findings, combining SRS with immunotherapy might potentially delay the necessity for salvage radiotherapy in cases of distant brain recurrences. Ongoing trials, such as NCT03483012, are exploring the combination of SRS and immunotherapy in TNBC. Additionally, trials are investigating various immunotherapy strategies, including Pembrolizumab with SRS (NCT03483012), haploidentical hematopoietic stem cells, and dendritic vaccines (NCT01782274, NCT03638765, NCT04711824, NCT04789668) [24]. In the future, the patient's systemic treatments may influence the decision between SRS and WBRT.

While antigens in the CNS were traditionally thought to be incapable of triggering an inflammatory immune response, emerging evidence challenges this notion [25]. Studies evaluating the efficacy of immunotherapy in brain metastases predominantly focus on lung and melanoma [26,27]. Unfortunately, despite rationale for intracranial efficacy of immunotherapy particularly among patients with triple negative, programmed death-ligand 1 (PD-L1) positive metastatic breast cancer, patients with brain metastases were not well represented in relevant phase III randomized controlled trials. In the context of triple negative breast cancer (BC), the subgroup analysis of the IMpassion130 clinical trial, investigating the immune checkpoint inhibitor (ICI) atezolizumab combined with nab-paclitaxel, did not reveal a significant benefit for patients with brain metastases which was 6 % of the patients [28]. Due to limited data in the literature, our study suggested that it is important to evaluate the results of the combination of immunotherapy and SRS in patients with brain metastases diagnosed with pure TNBC.

In the literature, distant brain recurrence rates and salvage RT ratios after SRS have been found to be higher and detected earlier in patients with triple-negative breast cancer compared to other groups ($p = 0.032$) [18,29,30]. For this reason, SRS is recommended, particularly in patients with a longer life expectancy [29,31]. In our study, distant brain control rates after SRS were comparable to those reported for other primary brain metastases in the literature [11,15–17]. Studies have shown distant brain control rates ranging from 45 % to 73 % at 1 year for brain metastases from various primaries [11,15–17]. Similarly, in our series, we achieved a distant brain control rate of 76 % after SRS in triple-negative breast cancer patients with 1–10 brain metastases. However, due to the scarcity of OS data specifically for pure TNBC in the literature, when compared to breast cancer brain metastases across all histological groups, a lower overall survival was observed. This observation is consistent with the generally poor prognosis linked to metastatic pure triple-negative breast cancer [18,29]. Our study indicates

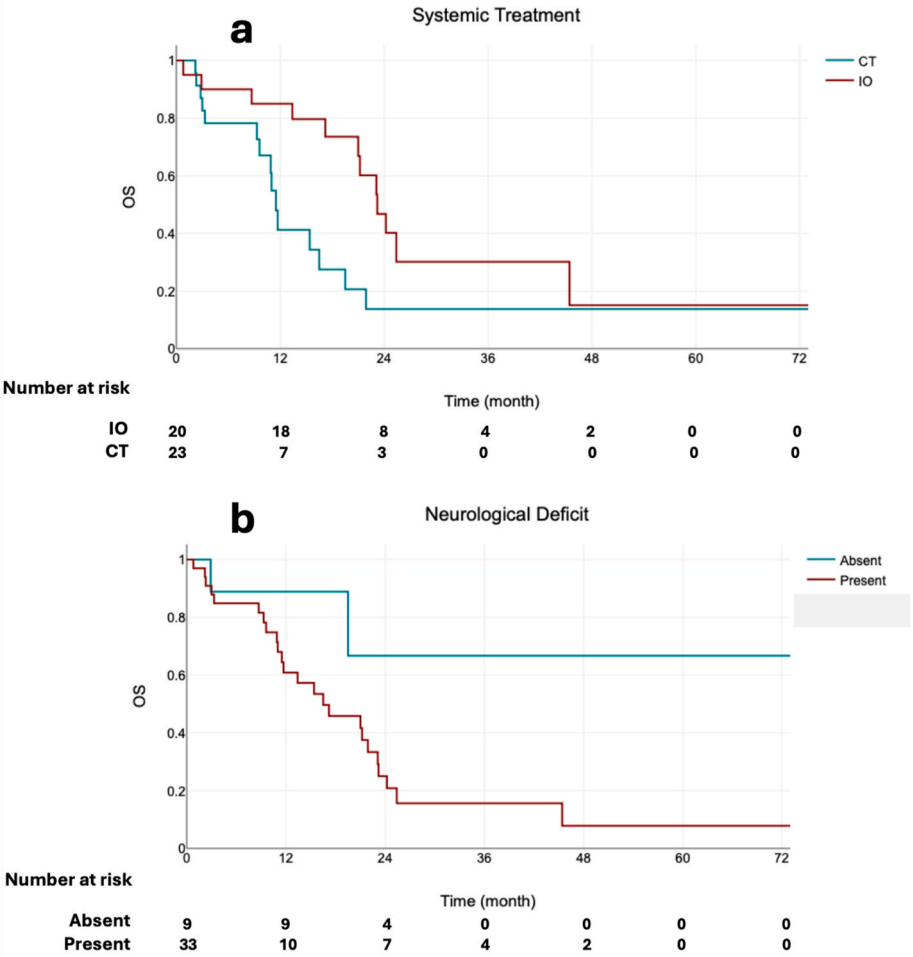

Fig. 3. Overall survival by systemic treatment type (a) and neurological deficit (b).

that although SRS may effectively control brain metastases in TNBC patients, mortality may still be influenced by extracranial metastases.

One of the primary limitations of this study is its retrospective nature and the restricted number of patients with heterogeneous SRS doses. Additionally, recurrence definitions were not centrally assessed but rather evaluated within each hospital's tumor board. The exclusion of potentially poorer-prognosis patients who initially underwent WBRT could influence the outcomes, contributing to a potential bias in the results. Furthermore, the selection of systemic treatments was at the discretion of the treating physician. Given the unknown parameters such as the number and sequence of prior systemic treatments, as well as the PD-L1 receptor status in primary tumor and brain metastases, these factors could potentially confound the outcomes in this retrospective analysis.

6. Conclusion

SRS demonstrates favourable outcomes in terms of local control and distant brain metastasis-free survival patients with TNBC. Neurological deficit and immunotherapy use significantly influence overall survival, emphasizing the importance of personalized treatment approaches and MRI surveillance based on these factors.

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CRediT authorship contribution statement

Menekse Turna: Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Berna Akkus Yıldırım:** Writing – review & editing, Supervision, Methodology. **Çakır Numanoglu:** Data curation. **Mustafa Halil Akboru:** Methodology, Data curation. **Rashad Rzazade:** Data curation. **Hale Başak Çağlar:** Writing – review & editing, Supervision.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2024.103757.

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