Jour Radiat Oncol Palliat. 2026; 10(1):1-15

ORIGINAL ARTICLE **/ /Open Access //**

Prognostic Factors Following Palliative Radiotherapy in Breast Cancer Patients with Oligometastatic Disease Limited to One or Two Metastatic Lesions: A Single-Center Retrospective Study

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Abstract

Background: *Radiotherapy plays an increasingly important role in the management of oligometastatic breast cancer (OMBC); however, prognostic factors associated with treatment outcomes remain incompletely defined. This study evaluated the clinical efficacy of radiotherapy and investigated clinical, pathological, and dosimetric factors associated with survival and local control in patients with OMBC limited one or two metastatic lesions.*

Methods: *Nineteen patients with OMBC limited to one or two metastatic lesins treated with metastasis-directed radiotherapy between 2019 and 2025 were retrospectively analyzed. Clinical characteristics, molecular subtype, gross tumor volume (GTV), planning target volume (PTV), radiotherapy dose, fractionation schedule, and biologically effective dose (BED) were evaluated. Treatment response was assessed according to RECIST criteria. Overall survival (OS), progression-free survival (PFS), and local control (LC) were estimated using the Kaplan–Meier method. Prognostic factors were analyzed using the log-rank test and Spearman correlation analysis.*

Results: *The median follow-up was 35 months. The objective response rate (CR+PR) was 90%, including complete response in 53% of patients, partial response in 37%, and stable disease in 5%. Median OS, PFS, and LC were 35, 18, and 24 months, respectively. Patients with smaller PTVs (<100 cc) achieved higher complete response rates (86% vs. 33%), longer PFS (46 vs. 14 months), and superior local control (36 vs. 14 months, p=0.018) compared with those with PTVs >200 cc. PTV was significantly associated with LC (p=0.007) and demonstrated a moderate inverse correlation with PFS (Spearman's ρ = −0.508, p=0.026). Higher BED (>55 Gy) was associated with improved radiological response and longer PFS; however, these differences did not reach statistical significance. Age, ER expression, PR expression, Ki-67 index, GTV, radiotherapy dose, and fractionation schedule were not significantly associated with OS, PFS, or LC in OMBC with one or two metastatic lesions .*

Conclusions: Palliative radiotherapy provided high local response rates and durable disease control in patients with oligometastatic breast cancer limited to one or two metastatic lesions. Smaller PTV volumes were significantly associated with longer PFS and improved local control, suggesting that irradiated tumor volume may be an important prognostic factor in this setting. Higher BED and favorable molecular subtype, particularly Luminal A disease, were also associated with more favorable outcomes. These findings support the potential role of radiotherapy in selected patients

with limited metastatic breast cancer, although larger prospective studies are warranted to validate these prognostic factors.

Keywords: *oligometastatic breast cancer; radiotherapy; planning target volume; local control; progression-free survival; overall survival; treatment response.*

Conflict of Interest:*There is no conflict on interest between companies or others*

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Received 12.07.2026 Accepted 27.08.2026

Introduction

The concept of oligometastatic disease**,** first introduced by Hellman and Weichselbaum, describes an intermediate biological state between localized and widely metastatic cancer, in which a limited number of metastatic lesions may still be amenable to curative local therapy [1]. Building on this concept, the current ESTRO/ASTRO consensus defines oligometastatic disease as the presence of one to five metastatic lesions that can be safely treated with local ablative therapy and accurately identified using modern high-resolution imaging techniques [2]. However, anatomical imaging alone may not fully reflect the true extent of systemic disease, as patients with an identical number of metastatic lesions may exhibit markedly different biological behaviors. Emerging evidence suggests that molecular characteristics, including circulating biomarkers and microRNA expression profiles, may improve patient selection for local ablative therapies, although no validated biomarkers are currently available for routine clinical practice.

Furthermore, the recently proposed ESTRO/EORTC dynamic classification distinguishes several clinical scenarios—including de novo oligometastatic disease**,** oligorecurrence**,** oligopersistence**,** and oligoprogression—according to disease history, response to systemic therapy, and disease-free interval, thereby providing a more biologically meaningful framework for clinical decision-making and future research [2,3].

Radiotherapy has long been an essential component of the multidisciplinary management of metastatic breast cancer. Traditionally, its primary role has been palliative, providing effective symptom relief for patients with painful bone metastases, spinal cord compression, brain metastases, and other symptomatic lesions while improving quality of life. Randomized trials, including the Dutch Bone Metastasis Study and RTOG 97-14, demonstrated that different dose-fractionation schedules provide comparable pain relief and local symptom control, establishing radiotherapy as the standard local treatment for metastatic disease.

Consequently, current ASTRO and ESTRO guidelines recommend palliative radiotherapy as a safe, effective, and well-tolerated treatment for symptomatic metastatic lesions. Beyond symptom palliation, advances in radiotherapy techniques have enabled the delivery of higher, more conformal doses with improved normal tissue sparing, expanding its role from symptom control toward durable local tumor eradication in selected patients [4-7].

The recognition of oligometastatic disease as a distinct biological state has further broadened the role of radiotherapy. Oligometastatic breast cancer, generally defined as the presence of up to five metastatic lesions, represents an intermediate stage between localized and widely disseminated disease, in which aggressive local treatment may delay disease progression and improve long-term outcomes. Prospective studies such as SABR-COMET, together with disease-specific trials including NRG-BR002 and AVATAR, have demonstrated that metastasis-directed radiotherapy can achieve excellent local control and may prolong progression-free survival in carefully selected patients. However, despite these encouraging results, considerable uncertainty remains regarding the optimal patient selection criteria, appropriate radiation dose and fractionation, and the prognostic significance of volumetric parameters such as gross tumor volume (GTV) and planning target volume (PTV). Therefore, further clinical evidence is needed to better define the factors associated with treatment response and survival following radiotherapy in patients with oligometastatic breast cancer [8-10].

The role of stereotactic body radiotherapy (SBRT) in oligometastatic breast cancer (OMBC) has evolved considerably over the past decade.

Early retrospective and prospective studies by Milano et al., Trovo et al., Scorsetti et al., Yoo et al., and Weykamp et al. consistently demonstrated excellent local control rates exceeding 90%, with very low rates of grade ≥3 toxicity, establishing SBRT as a safe and highly effective local ablative treatment.

These studies also identified several favorable prognostic factors, including younger age, good performance status, hormone receptor-positive disease, limited metastatic burden, bone-only metastases, and comprehensive treatment of all detectable metastatic lesions. Nevertheless, despite excellent local tumor control, distant progression remained the predominant pattern of treatment failure, emphasizing the importance of occult micrometastatic disease and supporting the concept that SBRT should complement, rather than replace, effective systemic therapy [11-15].

The encouraging results of the SABR-COMET trial generated substantial enthusiasm for metastasis-directed therapy across multiple tumor types. In this landmark randomized phase II study, Palma et al. demonstrated significant improvements in both progression-free survival and overall survival following comprehensive stereotactic ablative radiotherapy directed to all metastatic sites. Although breast cancer represented only a small subgroup of the study population, SABR-COMET provided the first high-level randomized evidence supporting the biological rationale for aggressive local treatment in oligometastatic disease [8].

The SABR-COMET trial enrolled 99 patients with controlled primary tumors and one to five metastatic lesions arising from a variety of solid malignancies, including breast, lung, colorectal, and prostate cancers. Participants were randomized to receive either standard systemic therapy alone or standard systemic therapy combined with SABR targeting all metastatic lesions.

After a median follow-up of 51 months, the addition of SABR significantly improved long-term clinical outcomes. Five-year overall survival increased from 17.7% to 42.3%, while five-year progression-free survival improved from

3.2% to 17.3%**.** Importantly, these survival gains were achieved without compromising quality of life or increasing late treatment-related toxicity, further supporting the safety of comprehensive metastasis-directed therapy [8].

Although only 18 patients with breast cancer were included in SABR-COMET, the study established the proof-of-concept that eradication of all radiographically visible metastatic lesions may alter the natural history of oligometastatic disease. However, because the trial included multiple tumor histologies and was not powered for disease-specific subgroup analyses, its findings cannot be directly extrapolated to metastatic breast cancer. Consequently, several breast cancer-specific randomized trials, including NRG-BR002, EXTEND**,** and AVATAR, were subsequently initiated to clarify the role of SBRT in this patient population [8].

Subsequently, the breast cancer-specific NRG-BR002 trial, conducted by Chmura et al.**,** failed to demonstrate significant improvements in progression-free survival or overall survival despite achieving excellent local control of irradiated lesions. These findings highlighted that durable local control alone may be insufficient to improve survival in biologically heterogeneous metastatic breast cancer [9].

An important observation from NRG-BR002 was that approximately 40% of first disease progressions occurred as newly developed metastatic lesions outside the previously treated sites in both treatment arms. This observation suggests that occult systemic dissemination, rather than failure of local therapy, remains the principal mechanism of disease progression. Therefore, although SBRT effectively eradicates visible metastatic deposits, its survival benefit is likely to depend on careful biological patient selection and integration with modern systemic therapies [9].

One of the major limitations of NRG-BR002 is that patient selection relied primarily on the number of residual metastatic lesions following systemic therapy rather than on the underlying biological subtype of oligometastatic disease. Consequently, patients with true de novo oligometastatic disease and those with induced oligopersistent disease were analyzed together despite potentially distinct tumor biology and prognosis. This biological heterogeneity may have diluted any potential survival benefit associated with metastasis-directed therapy [9].

Likewise, the randomized EXTEND trial conducted by Reddy et al**.** demonstrated excellent local control but failed to show a significant improvement in progression-free survival following the addition of metastasis-directed therapy to standard systemic treatment. Disease progression continued to occur predominantly at previously untreated distant sites, reinforcing the concept that occult systemic disease remains the major determinant of long-term clinical outcomes [16].

The EXTEND trial, conducted by Reddy et al.**,** was one of the first randomized phase II studies to evaluate whether the addition of metastasis-directed therapy (MDT), primarily SBRT, to standard systemic therapy could improve clinical outcomes in patients with oligometastatic breast cancer. Patients with five or fewer metastatic lesions were randomly assigned to receive either standard systemic therapy alone or standard systemic therapy combined with definitive local treatment to all metastatic sites. The primary endpoint was progression-free survival (PFS), whereas secondary endpoints included overall survival (OS), time to initiation of subsequent systemic

therapy, time to development of new metastatic lesions, quality of life, and immunologic outcomes [16].

A total of 43 patients were included in the study (22 receiving MDT plus systemic therapy and 21 receiving systemic therapy alone), with a median follow-up of 24.8 months. Contrary to expectations, the addition of metastasis-directed therapy did not significantly improve progression-free survival. Median PFS was 15.6 months in the MDT group compared with 24.9 months in the standard systemic therapy group, with no statistically significant difference between the treatment arms. Similarly, no meaningful differences were observed in overall survival, time to subsequent systemic therapy, development of new metastatic lesions, quality of life, or systemic immune response [16].

The investigators emphasized that these findings should be interpreted cautiously because of the relatively small sample size, the biological heterogeneity of the study population, and the unexpectedly favorable outcomes observed in both treatment groups. Consequently, the EXTEND trial does not support the routine incorporation of SBRT into systemic therapy for an unselected population of patients with oligometastatic breast cancer. Instead, the results reinforce the need for improved biological stratification and more precise patient selection in future randomized studies [16].

Increasing attention has recently focused on oligoprogressive disease**,** in which only a limited number of metastatic lesions progress while the remaining disease continues to be controlled by ongoing systemic therapy. In this clinical setting, SBRT offers the opportunity to eradicate resistant metastatic clones while allowing continuation of an otherwise effective systemic regimen, thereby potentially delaying treatment escalation [17].

The Consolidative Use of Radiotherapy to Block (CURB) trial, led by Tsai et al.**,** was the first randomized phase II study specifically designed to evaluate SBRT in patients with oligoprogressive metastatic breast cancer and non-small cell lung cancer. Patients presenting with five or fewer progressing metastatic lesions during otherwise effective systemic therapy were randomized to either continue systemic therapy alone or receive SBRT to all progressing lesions while maintaining the same systemic treatment. The underlying hypothesis was that elimination of resistant metastatic clones could prolong disease control and postpone the need for subsequent lines of systemic therapy [17].

Overall, 106 patients were enrolled, including 47 patients with breast cancer and 59 with non-small cell lung cancer**.** In the overall study population, SBRT significantly improved progression-free survival. However, this benefit was driven almost entirely by the non-small cell lung cancer cohort. In contrast, patients with breast cancer experienced no statistically significant improvement in progression-free survival or overall survival despite excellent local control and a favorable toxicity profile [17].

Exploratory molecular analyses suggested that progression in breast cancer was more frequently associated with the development of new metastatic lesions, whereas progression in non-small cell lung cancer predominantly occurred within pre-existing metastatic sites. These observations provide a plausible biological explanation for the differential treatment effect observed between tumor types and further support the concept that metastatic breast cancer often represents

a systemic rather than purely localized process.

Consequently, current evidence does not support the routine application of SBRT for all patients with oligoprogressive breast cancer; instead, treatment decisions should be individualized through multidisciplinary evaluation and integrated with effective systemic therapy [17].

More encouraging findings have emerged from studies evaluating SBRT in carefully selected patients with oligoprogressive hormone receptor-positive/HER2-negative breast cancer receiving modern targeted systemic therapy. Among these, the TROG 20.03 AVATAR trial, reported by David et al.**,** represents one of the most important prospective investigations in this setting [10].

The AVATAR trial was a prospective, multicenter phase II study evaluating whether stereotactic ablative body radiotherapy (SABR) could delay the need to modify systemic treatment in patients receiving a CDK4/6 inhibitor combined with an aromatase inhibitor. Eligible patients had up to five oligoprogressive metastatic lesions**,** all of which were treated with SABR while continuation of the same systemic therapy was maintained. Unlike previous randomized studies that focused primarily on progression-free survival, AVATAR selected event-free survival (EFS) as its primary endpoint. Events were defined as the need to change systemic therapy, disease progression within six months, or the development of more than three additional progressive lesions. This endpoint better reflects current treatment strategies aimed at maximizing the duration of effective targeted therapy [10].

The AVATAR trial demonstrated encouraging clinical activity. Nearly half of the enrolled patients remained on the same CDK4/6 inhibitor-based regimen for at least six months following SABR, thereby meeting the predefined primary endpoint. Furthermore, repeat SABR was permitted for subsequent episodes of oligoprogression, allowing prolonged disease control without immediate escalation to next-line systemic therapy. Treatment was well tolerated, with minimal high-grade toxicity, confirming the safety and feasibility of integrating SABR into the management of oligoprogressive hormone receptor-positive/HER2-negative breast cancer[10].

Although AVATAR was limited by its single-arm design**,** relatively small sample size, and absence of a randomized comparator, it provides important prospective evidence supporting the concept that metastasis-directed radiotherapy can prolong the clinical benefit of contemporary endocrine-targeted therapy in carefully selected patients. These findings establish an important foundation for future randomized trials investigating biologically selected populations with oligoprogressive breast cancer [10].

Although OMBC has been evaluated in several previous studies, most have included patients with a broader range of metastatic burden. In contrast, the present study specifically focused on a highly selected population with oligometastatic breast cancer limited to one or two metastatic lesions. By restricting the metastatic burden to a maximum of two lesions, we aimed to investigate the prognostic impact of clinical, biological, and dosimetric factors in this distinct subgroup and to identify factors associated with treatment response, progression-free survival, and local control following radiotherapy.

MATERIAL AND METHODS

Patients and Tumor Characteristics

A total of 19 patients with who underwent SBRT in OMBC with one or two metastatic lesions were included in this retrospective study. Patient demographics, clinical and pathological different characteristics, and treatment-related data were collected from institutional medical records. The median age at the time of SBRT was 50 years (interquartile range [IQR], 46.5–54.5 years; range, 27–86 years).

All patients had histologically confirmed breast cancer with oligometastatic disease. Hormone receptor status was assessed based on estrogen receptor (ER) and progesterone receptor (PR) expression. The median ER expression was 70%, and the median PR expression was 30%. The median Ki-67 proliferation index was 30%.

According to molecular subtype classification, luminal B breast cancer was the most frequent subtype, observed in 8 patients (42.1%), followed by luminal A in 6 patients (31.6%), HER2-positive disease in 3 patients (15.8%), and triple-negative breast cancer in 2 patients (10.5%).

Table 1. Patient and Tumor Characteristics of Patients with Oligometastatic Breast Cancer (n=19)

Variable	Value
Age (years)	
Median age (IQR)	50 (46.5–54.5)
Range	27–86
Hormone receptor status	
Median ER expression (%)	70
Median PR expression (%)	30
Median Ki-67 index (%)	30
Molecular subtype	n (%)
Luminal B	8 (42.1)
Luminal A	6 (31.6)
HER2-positive	3 (15.8)
Triple-negative breast cancer	2 (10.5)

Values are presented as median (interquartile range [IQR]) or number (%), as appropriate.

RT Characteristics and Treatment Outcomes

Hypofractionated or SBRT was delivered to oligometastatic lesions using image-guided radiotherapy techniques. Treatment planning was performed based on simulation imaging, and target volumes were delineated according to institutional protocols. The median gross tumor volume (GTV) was 3.2 cc (interquartile range [IQR], 1.8–13.6 cc), while the median planning target volume (PTV) was 114 cc (IQR, 67–200.5 cc).

Patients were followed longitudinally for oncological outcomes, including overall survival (OS), progression-free survival (PFS), and local control (LC). The median follow-up duration was reflected by a median OS of 35 months (IQR, 30–51.5 months). The median PFS was 18 months (IQR, 14–33.5 months), and the median duration of local control following RT was 24 months (IQR, 15–33.5 months).

Tumor volume parameters and clinical outcomes were subsequently evaluated to investigate potential associations between

RT-treated lesion characteristics and treatment efficacy.

Table 2. RT Characteristics and Oncologic Outcomes (n=19)

Variable	Value
Target volume parameters	
Median GTV, cc	3.2 (1.8–13.6)
Median PTV, cc	114 (67–200.5)
Met.lesion number 1	18
Met.lesion number 1	1
Survival outcomes	
Median OS), months	35 (30–51.5)
Median PFS, months	18 (14–33.5)
Median LC duration, months	24 (15–33.5)

Values are presented as median (interquartile range [IQR]).
GTV: Gross tumor volüme: PTV: Planning target volüme OS: Overall surviva PFS: Progression free survival

Results

The objective response rate (CR+PR) was 90%; the complete response (CR) rate was 53% (n=10), the partial response (PR) rate was 37% (n=7), and the stable disease (SD) rate was 5% (n=1). Median overall survival (OS) was 46 months, median progression-free survival (PFS) was 18 months, and median local control duration was 20 months.

PTV volume analysis revealed clinically significant differences: in the small PTV group (<100 cc, n=7), the CR rate was 86% and median PFS was 46 months, whereas in the large PTV group (>200 cc, n=6), the CR rate was 33% and median PFS was 14 months. In terms of BED analysis, the CR rate was 75% and median PFS was 37 months in patients receiving BED >55 Gy, whereas in the BED <30 Gy group, the CR rate was 50% and median PFS was 15 months. In the molecular subtype comparison, the best outcomes were observed in the Luminal A group, with a 100% CR rate and a median PFS of 54 months. In de novo oligometastatic disease, the median PFS was 24 months, whereas in the metachronous group, it was 15 months.

The association between clinical, biological, and dosimetric parameters and oncological outcomes was evaluated. No significant association was observed between age, estrogen receptor (ER) expression, progesterone receptor (PR) expression, Ki-67 index, or gross tumor volume (GTV) and overall survival (OS), progression-free survival (PFS), or local control (LC) duration.

The median OS was 35 months, with no significant differences according to age (p=0.436), ER expression (p=0.129), PR expression (p=1.000), Ki-67 index (p=0.219), GTV (p=0.190), or PTV volume (p=0.539) and metastatic lesion number . Similarly, no significant associations were observed between these variables and PFS, although higher Ki-67 values and larger GTVs demonstrated a trend toward shorter PFS (p=0.076 and p=0.066, respectively).

A significant association was identified between planning target volume (PTV) and local control outcomes. PTV volume showed a significant inverse correlation with PFS (Spearman's $\rho = -0.508$, p=0.026), indicating that larger irradiated volumes were associated with shorter

progression-free survival. In addition, PTV was significantly associated with local control duration (p=0.007). Patients with smaller PTV volumes (<100 cc) demonstrated longer local control compared with those with larger PTV volumes (>200 cc) (36 vs. 14 months, p=0.018).

Among patients with available follow-up data, local control was achieved in 15 of 19 patients (78.9%). The median duration of local control was 24 months. Patients with smaller target volumes showed higher local control rates compared with those with larger PTV volumes (100% vs. 60%).

Table 3. Factors Associated with Overall Survival, Progression-Free Survival, and Local Control

Variable	n (%) / Median (IQR)	OS (months)	p	PFS (months)	p	LC (months)	p	ORR/LC (%)	Spearman OS	Spearman PFS
Age	50 (46.5–54.5)	38.5 / 35	0.436	18.5 / 18	0.967	27 / 24	0.870	–	–	–
ER (%)	70 (45–80)	31.5 / 44	0.129	19 / 16	1.000	22 / 30	0.595	–	–	–
PR (%)	30 (17.5–50)	33 / 39.5	1.000	20 / 15.5	0.741	24 / 19.5	0.508	–	–	–
Ki-67 (%)	30 (22.5–40)	47 / 33	0.219	23 / 14	0.076	30 / 18	0.138	–	–	–
GTV (cc)	3.2 (1.8–13.6)	47 / 33	0.190	23 / 14	0.066	27 / 24	0.287	–	–	–
PTV (cc)	114 (67–200.5)	39.5 / 33	0.539	27.5 / 15	0.094	**31.5 / 15**	**0.007**	–	ρ=−0.210 (0.387)	**ρ=−0.508 (0.026)**
PTV <100 vs >200 cc	7 / 5	54 / 33	0.432	34 / 15	0.122	36 / 14	0.018	**100% vs 60%**	–	–
Local control	**15/19 (78.9%)**	–	–	–	–	Median 24 ay	–	**78.9%**	–	–

Association of Radiation Dose and Fractionation with Clinical Outcomes

Spearman correlation analysis was performed to evaluate the association between RT dose parameters and clinical outcomes. No significant correlation was observed between radiation dose and overall survival (ρ = −0.029, p = 0.905), progression-free survival (ρ = 0.285, p = 0.238), or local control (ρ = 0.216, p = 0.374). Likewise, the number of fractions was not significantly correlated with overall survival (ρ = −0.078, p = 0.752), progression-free survival (ρ = −0.210, p = 0.389), or local control (ρ = −0.196, p = 0.421). These findings indicate that neither radiation dose nor fractionation schedule was significantly associated with treatment outcomes in this cohort that OMBC limited to one or two lesions.

Discussion

Metastasis-directed therapy (MDT), particularly stereotactic body radiotherapy (SBRT), has emerged as a promising treatment strategy for patients with oligometastatic breast cancer. Nevertheless, the currently available randomized evidence has produced inconsistent results, indicating that the clinical benefit of SBRT is strongly influenced by patient selection, tumor biology, and the clinical setting in which treatment is delivered.

The SABR-COMET trial provided the first randomized evidence supporting comprehensive local ablative treatment in oligometastatic disease. Although only a limited number of patients with breast cancer were included, Palma et al.

demonstrated significant improvements in both progression-free and overall survival without compromising quality of life. These findings established the biological proof-of-concept that eradication of all radiographically detectable metastatic lesions may alter the natural history of oligometastatic disease in carefully selected patients [8].

In contrast, breast cancer-specific randomized studies have produced less encouraging results. Both the NRG-BR002 trial and the EXTEND trial failed to demonstrate a significant improvement in progression-free or overall survival despite achieving excellent local control of treated lesions [9,16]. Importantly, these studies consistently showed that disease progression most frequently occurred through the development of new metastatic lesions**,** rather than recurrence within irradiated sites. This observation suggests that occult systemic dissemination, rather than inadequate local treatment, remains the principal determinant of long-term outcome in many patients with oligometastatic breast cancer.

The apparent discrepancy between the positive findings of SABR-COMET and the neutral results of NRG-BR002 and EXTEND is likely multifactorial. First, breast cancer represents a biologically heterogeneous disease comprising distinct molecular subtypes with markedly different patterns of metastatic spread and treatment sensitivity. Second, contemporary systemic therapies—including CDK4/6 inhibitors, HER2-directed agents, antibody-drug conjugates, PARP inhibitors, and modern endocrine therapies—have substantially improved disease control, thereby reducing the incremental benefit that may be achieved through local ablative treatment alone. Finally, the relatively small sample sizes and favorable prognoses observed in both treatment arms of the randomized breast cancer-specific studies may have limited their ability to detect clinically meaningful survival differences [9,16].

An additional limitation shared by most published studies is the reliance on anatomical definitions of oligometastatic disease. Current classifications are primarily based on the number of metastatic lesions rather than their biological behavior. However, patients with an identical metastatic burden may have profoundly different metastatic potential. As emphasized by Shien et al.**,** oligometastatic breast cancer should be regarded as a distinct biological entity rather than merely a numerical stage of metastatic disease. The distinction between de novo oligometastatic disease**,** oligorecurrence**,** oligopersistence**,** and oligoprogression is increasingly recognized as clinically relevant because these conditions differ in prognosis, treatment objectives, and expected response to metastasis-directed therapy [2,3].

Accordingly, future patient selection should extend beyond conventional imaging findings. Integration of circulating tumor DNA (ctDNA), genomic profiling, molecular signatures, circulating biomarkers, and advanced functional imaging techniques, including PET/CT and whole-body MRI, may improve identification of patients with truly limited metastatic potential who are most likely to derive durable benefit from SBRT [2,3].

The management of oligoprogressive disease deserves particular attention. Unlike patients with untreated oligometastatic disease, these patients have already demonstrated prolonged disease control with systemic therapy, with progression limited to only a small number of resistant metastatic sites. In this setting, SBRT may eradicate resistant

tumor clones while allowing continuation of otherwise effective systemic therapy. The CURB trial demonstrated that this strategy did not significantly improve outcomes in the breast cancer subgroup, whereas the AVATAR trial suggested that carefully selected patients with hormone receptor-positive/HER2-negative disease receiving CDK4/6 inhibitor-based therapy may experience meaningful delays in systemic treatment escalation following SBRT. Although these studies evaluated different patient populations and employed different study designs, together they support the concept that the greatest value of SBRT may lie in preserving the efficacy of contemporary systemic therapy**,** rather than directly improving overall survival **[**10, 17].

Taken together, the available evidence suggests that the principal benefit of SBRT in metastatic breast cancer extends beyond durable local tumor control. SBRT may prolong the duration of effective systemic therapy, delay treatment escalation, preserve quality of life, and maintain disease control in carefully selected patients. However, its routine application in all patients with oligometastatic breast cancer is not supported by the current randomized evidence.

The high objective response rate observed in the present study is consistent not only with SBRT series but also with previous reports evaluating conventionally fractionated radiotherapy for metastatic breast cancer. Radiotherapy has long been recognized as an effective local treatment for metastatic lesions, providing durable symptom relief together with high local response rates. The prospective RAPASH study by Lutz et al. **[**4,7**]** demonstrated that palliative radiotherapy achieved excellent symptom control with durable local responses in patients with painful bone metastases. Similarly, the Dutch Bone Metastasis Study by Steenland et al. [5] and the randomized trial by Hartsell et al**.** [6] confirmed that radiotherapy provides effective local disease control irrespective of fractionation schedule. Although these studies primarily evaluated symptom palliation rather than oligometastatic disease, they established radiotherapy as a highly effective local modality capable of achieving substantial tumor regression.

Our findings further suggest that tumor burden rather than radiation dose may be the principal determinant of outcome. Planning target volume (PTV <100 vs >200 cc) was the only parameter significantly associated with local control and progression-free survival, whereas radiation dose and fractionation did not significantly influence survival outcomes. Similar observations have been reported in metastatic breast cancer cohorts receiving conventionally fractionated radiotherapy, where lesion size and metastatic burden consistently predicted treatment outcome more strongly than prescribed radiation dose. Milano et al. [11] likewise reported that smaller metastatic lesions experienced superior local control following ablative radiotherapy, suggesting that disease volume remains a dominant prognostic factor regardless of the radiotherapy technique employed.

Although higher biologically effective doses tended to produce higher complete response rates and longer progression-free survival in our cohort, these differences did not reach statistical significance. This observation may reflect the limited statistical power of the present study rather than the absence of a biological dose-response relationship. Previous randomized studies comparing different palliative fractionation

schedules, including those by Hartsell et al. [6], Steenland et al. [5], and the ASTRO Evidence-Based Guideline [7], demonstrated comparable local efficacy among several dose schedules for uncomplicated metastatic lesions. These findings support the concept that appropriate patient selection and disease characteristics may be more influential than modest differences in radiation dose in determining clinical outcomes.

The favorable outcomes observed in patients with Luminal A disease and those presenting with de novo oligometastatic disease are consistent with current evidence emphasizing the importance of tumor biology. The ESTRO–EORTC consensus by Guckenberger et al. **[**2**]** highlighted favorable molecular subtype and limited disease burden as essential criteria for selecting candidates for metastasis-directed radiotherapy. Likewise, the AVATAR trial reported by Foroudi et al**.** [10] demonstrated prolonged disease control in hormone receptor-positive oligoprogressive breast cancer treated with radiotherapy while maintaining systemic therapy, underscoring the importance of integrating biological characteristics with local treatment strategies.

Future prospective trials should therefore move beyond purely anatomical definitions of oligometastatic disease and incorporate molecular biomarkers, ctDNA, genomic profiling, advanced imaging, and dynamic assessment of treatment response into patient selection algorithms. Such biologically informed approaches are expected to identify the subgroup of patients most likely to achieve meaningful improvements in progression-free and overall survival following metastasis-directed therapy **[**2,3].

The negative findings of NRG-BR002 and EXTEND highlight an important limitation of current patient selection strategies, which rely predominantly on anatomical definitions of oligometastatic disease. Increasing evidence suggests that biological markers may better identify patients who harbor occult systemic disease and are therefore less likely to benefit from aggressive local therapy [9,16].

The studies demonstrated to metastasis-directed therapies, particularly stereotactic body radiotherapy (SBRT), may provide high rates of local control and allow continuation of effective systemic therapy in selected patients with oligometastatic or oligoprogressive breast cancer. However, current randomized evidence does not yet demonstrate a definitive overall survival or progression-free survival benefit for metastasis-directed therapy in all patients. Therefore, treatment decisions should be individualized based on the number and location of metastases, tumor biology, overall disease burden, and response to systemic therapy [18].

Finally, biomarkers reflecting systemic tumor burden may further refine patient selection. As discussed in the present study, elevated D-dimer has been associated with cancer-related hypercoagulability, micrometastatic dissemination, and poorer survival across several malignancies.

It is therefore plausible that patients with markedly elevated D-dimer levels represent a biologically disseminated disease phenotype that is less likely to benefit from aggressive local ablative treatment, whereas patients with low D-dimer levels may more closely represent a true oligometastatic state.

Although this hypothesis remains speculative, it provides a biologically plausible rationale for prospective studies integrating D-dimer with molecular

biomarkers and clinical risk stratification to optimize selection for SBRT.

In this context, Kızıltan et al. demonstrated that elevated pre-radiotherapy D-dimer levels were independently associated with significantly worse overall survival and progression-free survival in patients receiving radiotherapy for breast cancer. Patients with low D-dimer levels experienced substantially longer survival, whereas elevated D-dimer identified individuals at higher risk of disease progression, suggesting that this inexpensive and widely available biomarker may reflect occult metastatic burden and aggressive tumor biology [19].

Similarly, Kimia Çepni et al. reported that increased D-dimer levels were associated with adverse oncological outcomes and may serve as a prognostic biomarker in breast cancer. Collectively, these findings support the hypothesis that biomarkers reflecting systemic tumor burden may complement imaging-based definitions of oligometastatic disease and improve patient selection for metastasis-directed therapy **[**20].

Taken together, future prospective trials should integrate clinical characteristics, molecular profiling, circulating tumor DNA, advanced imaging, and circulating biomarkers such as D-dimer to establish biologically driven treatment algorithms. Such an approach may identify patients with true oligometastatic disease who are most likely to derive durable benefit from SBRT while avoiding unnecessary local treatment in patients with biologically disseminated disease.

Conclusion

Radiotherapy provided excellent local tumor response and durable local control in patients with oligometastatic breast cancer, achieving a high objective response rate and favorable survival outcomes. Among the evaluated prognostic factors, planning target volume emerged as the strongest predictor of treatment outcome, with smaller target volumes being associated with significantly improved local control and longer progression-free survival. In contrast, radiation dose, fractionation schedule, and conventional clinicopathological parameters were not significantly associated with oncological outcomes, although higher biologically effective doses and lower Ki-67 values demonstrated favorable trends.

These findings suggest that metastatic tumor burden may be a more important determinant of treatment efficacy than radiation dose alone, emphasizing the importance of careful patient selection for metastasis-directed radiotherapy. Given the limited sample size and retrospective design, the absence of significant associations for several variables should be interpreted with caution, as the study may have been underpowered to detect moderate prognostic effects. Larger prospective, multicenter studies are warranted to validate these findings, define optimal radiotherapy dose-fractionation strategies, and integrate volumetric parameters with molecular characteristics to improve individualized treatment selection especially in patients with OMBC limited to one or two lesions. .

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