

## Role of radiotherapy in oligometastatic breast cancer: Review of the literature

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**Author contributions:** Beduk Esen CS wrote the main body of the manuscript; Gultekin M and Yildiz F provided guidance in the structure of the manuscript and reviewed the manuscript.

**Conflict-of-interest statement:** The authors have no conflict of interests to declare.

**Country/Territory of origin:** Turkey

**Specialty type:** Oncology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C, C  
Grade D (Fair): 0  
Grade E (Poor): 0

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### Abstract

Metastatic breast cancer has been historically considered as an incurable disease. Radiotherapy (RT) has been traditionally used for only palliation of the symptoms caused by metastatic lesions. However, in recent years the concept of oligometastatic disease has been introduced in Cancer Medicine as a clinical scenario with a limited number of metastases ( $\leq 5$ ) and involved organs ( $\leq 2$ ) with controlled primary tumor. The main hypothesis in oligometastatic disease is that locoregional treatment of primary tumor site and metastasis-directed therapies with surgery and/or RT may improve outcomes. Recent studies have shown that not all metastatic breast cancer patients have the same prognosis, and selected patients with good prognostic features as those younger than 55 years, hormone receptor-positive, limited bone or liver metastases, a low-grade tumor, good performance status, long disease-free interval ( $> 12$  mo), and good response to systemic therapy may provide maximum benefit from definitive treatment procedures to all disease sites. While retrospective and prospective studies on locoregional treatment in oligometastatic breast cancer demonstrated conflicting results, there is an increasing trend in favor of locoregional treatment. Currently, available data also demonstrated the improvements in survival with metastasis-directed therapy in oligometastatic breast cancer. The current review will discuss the concept of oligometastases and provide up-to-date information about the role of RT in oligometastatic breast cancer.

**Key Words:** Breast cancer; Oligometastatic; Radiotherapy; Locoregional treatment; Ablative therapy; Metastasis-directed therapy

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**Core Tip:** Radiotherapy (RT) has been traditionally used for only palliation of the

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**Received:** February 28, 2021

**Peer-review started:** February 28, 2021

**First decision:** April 27, 2021

**Revised:** May 5, 2021

**Accepted:** December 22, 2021

**Article in press:** December 22, 2021

**Published online:** January 24, 2022

**P-Reviewer:** Al-Afandi N, Huo Q

**S-Editor:** Gong ZM

**L-Editor:** Filipodia

**P-Editor:** Gong ZM



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**Citation:** Beduk Esen CS, Gultekin M, Yildiz F. Role of radiotherapy in oligometastatic breast cancer: Review of the literature. *World J Clin Oncol* 2022; 13(1): 39-48

**URL:** <https://www.wjgnet.com/2218-4333/full/v13/i1/39.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v13.i1.39>

## INTRODUCTION

Breast cancer is the most common cancer in females worldwide, with an estimated 276480 new cases, and the second most common cause of cancer death with an estimated 42170 deaths in 2020[1]. Metastasis at the time of diagnosis has been observed in 3%-10% of breast cancer patients and has been considered in the past unlikely to be cured[2]. However, the metastatic disease has a broad spectrum ranging from a single metastasis to widespread dissemination, and it has been observed that not all metastatic patients have the same prognosis.

The concept of oligometastases was first described by Hellman and Weichselbaum [3] in 1995, and they hypothesized that patients with oligometastases should be considered as candidates for curative therapeutic strategies. Oligometastases was described as a clinical scenario with a limited number of metastases (1 to 5) and involved organs ( $\leq 2$ ) with controlled primary tumors[3]. The exact number of metastasis for the concept of oligometastases has not been clearly defined yet; however, most studies evaluating oligometastatic disease included patients with five or less metastasis[4,5].

While the standard treatment for metastatic disease includes systemic therapy with or without palliative radiotherapy (RT), recent studies are evaluating the role of ablative therapies to metastases and locoregional treatment to the primary tumor site in oligometastatic breast cancer[6-9]. In recent years, the prognosis of breast cancer has improved with the introduction of novel systemic therapies, even in patients with metastatic disease[10,11]. Some patients with good prognostic features may achieve complete response for more than 5 years after systemic therapy[12]. Several factors affect the prognosis in breast cancer patients with oligometastatic disease as the disease-free interval between primary cancer and metastasis formation, number of metastatic lesions, metastatic sites, hormone receptor status, human epidermal growth factor 2 (Her2) status, and pN stage[13-15]. Systemic therapy and local treatment to both primary and metastatic lesions may improve outcomes in such selected patients with metastatic breast cancer. Herein, we will review the impact of RT in oligometastatic breast cancer for both metastatic and primary tumor sites.

## SHOULD WE PERFORM LOCOREGIONAL TREATMENT IN OLIGOMETASTATIC BREAST CANCER PATIENTS?

In the past, the locoregional treatment in metastatic breast cancer was believed to have a role only for palliation of the symptoms caused by the local progression of the tumor. However, beginning from the early 2000s, with the advent of novel systemic therapies as new chemotherapeutic agents, anti-HER2 agents, hormonal therapies, immunotherapies, and cyclin-dependent kinase inhibitors, the destiny of patients with metastatic breast cancer have changed. A significant number of patients showed at least good partial response both in the primary and metastatic sites, which led to questioning the idea of treating these patients with some form of locoregional treatment based on the idea that the primary tumor could be a source of reseeding of cancer outside the breast. The National Cancer Database study revealed that surgery

to the primary site when added to systemic therapy in patients with stage IV breast cancer significantly improved survival[16]. A similar retrospective study using the Surveillance, Epidemiology, and End Results database also showed that median survival was longer in metastatic breast cancer patients who had surgery to the primary site than patients who did not (36 mo *vs* 21 mo,  $P < 0.001$ )[17]. However, the prospective phase III ABCSG-28 POSYTIME trial that randomized metastatic breast cancer patients to surgery followed by systemic therapy or systemic therapy alone could not demonstrate an overall survival (OS) benefit for the surgery arm[18]. Another study from India randomized 350 patients with *de novo* metastatic breast cancer who had an objective tumor response after 6-8 courses of chemotherapy to locoregional treatment to primary or no locoregional treatment arms[19]. At a median follow-up of 23 mo, no statistically significant difference in OS was observed between treatment arms (19.2 mo *vs* 20.5 mo,  $P = 0.79$ ). However, locoregional treatment was associated with improved locoregional progression-free survival (PFS) but shorter distant PFS[19]. In another study by Soran *et al*[20], 274 treatment naïve metastatic breast cancer patients were randomized to receive locoregional treatment followed by systemic therapy *vs* systemic therapy alone. With a median follow-up of 55 mo, median survival was significantly longer in the locoregional treatment arm compared to patients with systemic therapy alone arm (46 mo *vs* 37 mo,  $P = 0.005$ ). Unplanned subgroup analysis of this study showed that improvement in survival was observed in patients with estrogen receptor/progesterone receptor positive, Her2 negative disease, younger than 55 years, and with solitary bone-only metastasis[20].

Several ongoing trials are evaluating the impact of locoregional treatment on survival in metastatic breast cancer. Early results of the ECOG E2108 trial that randomized 256 patients whose disease responded to initial systemic therapy, or stayed stable, to systemic therapy plus locoregional treatment or systemic therapy alone, showed that there was no significant difference in 3-year OS (68.4% *vs* 67.9%,  $P = 0.63$ ); however, the locoregional recurrence or progression was significantly higher in the systemic therapy alone arm (3-year rate 25.6% *vs* 10.2%, Gray test  $P = 0.003$ )[21]. Preliminary results of another multicentric prospective ongoing trial (TBCRC 013) evaluating the impact of surgery on OS in metastatic breast cancer patients who responded to first-line systemic therapy showed that the addition of surgery to systemic therapy had no impact on OS even in responders to first-line systemic therapy[22]. JCOG1017 PRIM-BC trial comparing surgery to primary plus systemic therapy with systemic therapy alone has completed accrual, and results of this trial are being expected[23]. Ongoing SUBMIT (NCT01392586) trial is also investigating whether upfront surgery in patients with metastatic breast cancer will result in an improvement of the 2-year survival compared to the survival achieved by systemic therapy and delayed local treatment or systemic therapy alone[24]. The details of prospective randomized trials investigating the role of locoregional treatment in metastatic breast cancer are given in Table 1. The final results of these prospective randomized studies will hopefully clarify the exact role of locoregional treatment in metastatic breast cancer patients.

There is no prospective randomized study comparing surgery with surgery plus RT or RT alone as a locoregional treatment in metastatic breast cancer. A retrospective study by Gultekin *et al*[7] evaluating the impact of locoregional treatment in 227 oligometastatic breast cancer patients showed that locoregional treatment per se did not affect OS and PFS, however, surgery and RT when used together improved OS and PFS. The authors also observed that patients with solitary metastasis had longer PFS than patients with multiple metastases. In another retrospective study, Le Scodan *et al*[8] compared 320 metastatic breast cancer patients who received exclusive locoregional RT with or without surgery with 261 metastatic breast cancer patients who did not receive locoregional treatment. In this study, 78% of patients had exclusive locoregional RT, and patients with locoregional treatment had longer 3-year OS rates (43.4% *vs* 26.7%,  $P < 0.001$ ). Although there was no statistically significant difference in locoregional treatment modalities regarding survival outcomes, multifactorial analysis in the Le Scodan *et al*[8] study showed that age at diagnosis, visceral metastases, involvement of multiple sites, endocrine treatment, and locoregional treatment were independent prognostic factors for OS[8]. Retrospective studies published within the last decade investigating the impact of locoregional treatment on primary tumor sites are detailed in Table 2.

There is still no consensus about the efficacy of locoregional treatment in metastatic breast cancer. There is again no consensus about the optimal treatment strategy as surgery alone or surgery plus RT or RT alone when locoregional treatment is indicated. Based on the available data, locoregional treatment may be offered to patients who have a long-life expectancy, such as those younger than 55 years, have

**Table 1** Prospective randomized phase III trials investigating the role of locoregional treatment in *de novo* metastatic breast cancer

Ref.	n	Treatment	Patients	Median follow-up (mo)	Outcomes
Khan <i>et al</i> [21] (ECOG-ACRIN E2108)	256	Primary systemic therapy: LRT ( <i>n</i> = 125); No LRT ( <i>n</i> = 131)	NR	59	3-yr OS: 68.4% vs 67.9%, <i>P</i> = 0.63 3-yr locoregional recurrence/progression: 10.2% vs 25.6%, <i>P</i> = 0.003
Fitzal <i>et al</i> [18] (ABCSC-28 POSITIVE)	90	Arm A: Primary surgery + systemic therapy ( <i>n</i> = 45) Arm B: Primary systemic therapy ( <i>n</i> = 45)	Arm A: More cT3 and cN2 tumors	37.5	Stopped early Median OS (mo): 34.6 vs 54.8, <i>P</i> = 0.267 Time to distant progression (mo): 13.9 vs 29.0, <i>P</i> = 0.0668
Soran <i>et al</i> [20] (MF07-01)	274	LRT + systemic therapy ( <i>n</i> = 138) Systemic therapy ( <i>n</i> = 136)	LRT arm: More ER/PR (+), less triple negative tumors	54.5 vs 55	Median OS (mo): 46 vs 37, <i>P</i> = 0.005 Unplanned subgroup analysis: Improvement in survival: ER/PR (+), HER2 (-), < 55 yr, solitary bone-only metastasis
Badwe <i>et al</i> [19] (NCT00193778)	350	Primary systemic therapy: LRT ( <i>n</i> = 173); No LRT ( <i>n</i> = 177)	Similar patient and tumor characteristics	23	Median OS (mo): 19.2 vs 20.5, <i>P</i> = 0.79 Median LR-PFS (mo): not attained vs 18.2, <i>P</i> < 0.0001 Median distant-PFS (mo): 11.3 vs 19.8, <i>P</i> = 0.012

NR: Not reported; LRT: Locoregional treatment; c: Clinic; T: Tumor; N: Node; ER: Estrogen receptor; PR: Progesterone receptor; OS: Overall survival; HER2: Human epidermal growth factor receptor 2; LR: Locoregional; PFS: Progression-free survival.

hormone receptor-positive, HER2 positive, bone or limited liver metastases, presence of a low-grade tumor, good performance status, good response to systemic therapy, and a limited number of metastases[8,25].

## SHOULD WE TREAT METASTASES IN OLIGOMETASTATIC BREAST CANCER PATIENTS?

Traditionally, the standard treatment is systemic therapy for metastatic breast cancer patients; however, long-term complete response with systemic therapy alone is rare [12]. Given that progression in metastatic breast cancer patients frequently occurs at sites of known metastases rather than new metastatic lesions, local ablative therapies to metastatic sites may provide therapeutic benefit[9,26]. In addition to surgery and radiofrequency ablation, stereotactic body RT (SBRT) or stereotactic ablative RT (SABR), which allows highly conformal dose distribution using high dose per fraction with a low number of fractions, may be used as local ablative therapies to metastases to prevent progression[26,27].

Response to systemic therapy is a significant prognostic factor in metastatic breast cancer[4]. In a retrospective study by Weykamp *et al*[28], the 2-year local control and OS rates were reported as 89% and 62%, respectively, in patients with oligometastatic disease. The authors also observed that solitary metastasis and young age were independent factors for PFS and OS, respectively[28]. In another study by Kobayashi *et al*[29], 75 oligometastatic breast cancer patients who had a complete or partial response after systemic therapy and treated with local therapy were retrospectively evaluated, and it was demonstrated that complete response or no evidence of disease rates were significantly better in patients with a single organ metastasis than with two organ metastases (*P* = 0.002)[29]. In this retrospective study, the multidisciplinary treatment improved OS compared to systemic therapy alone[29].

Few studies have investigated the role of SBRT as a local treatment of metastases in oligometastatic disease including metastatic breast cancer patients (Table 3)[4-6,9,26,28,30,31]. Studies in the literature showed that the maximum benefit from SBRT to all metastatic sites was provided in young patients whose primary breast cancer was controlled, with a limited number of metastases, low tumor volume, only bone metastases, good response to systemic therapy, long disease-free interval (> 12 mo), and hormone receptor-positivity[4,29,30].

**Table 2 Retrospective studies published within the last decade investigating the impact of locoregional treatment to the primary tumor site in de novo metastatic breast cancer**

Ref.	n	Treatment	Patient	Median follow-up (mo)	Outcomes
Ma <i>et al</i> [35]	987	Surgery (n = 463) No surgery (n = 524)	Surgery arm: More T1-2, HR-positive, solitary metastasis, bone only metastasis	NR	Median survival (mo): 45 vs 28, P < 0.001  Better survival in surgery after systemic therapy than primary surgery  Triple negative, brain metastases: No benefit of surgery
Lane <i>et al</i> [16] (NCDB)	24015	Systemic therapy alone (n = 13505) Surgery before systemic therapy (n = 4552) Systemic therapy before surgery (n = 5958)	Surgery after systemic therapy arm: Younger, more T3-4 and HR-negative	NR	Median OS (mo): 37.5 vs 49.4 vs 52.8, P < 0.001  RT: No impact on OS
Li <i>et al</i> [36] (SEER database)	20870	Surgery (n = 5779) No surgery (n = 15091)	Surgery arm: Younger, more T1-3, N+, Gr III, and less HR+  More chemo and RT received	NR	Surgery arm (± RT): Improved BCSS and OS (P < 0.001)
Pons-Tostivint <i>et al</i> [37]	4276	LRT (n = 1706): Surgery, RT or both  No LRT (n = 2570)	LRT arm: Younger, more solitary or bone-only metastases	45.3	Median OS (mo): HR-positive, HER2- negative: 61.6 vs 45.9, P < 0.001  HR-positive, HER2-positive: 77.2 vs 52.6, P = 0.008  Triple negative: 19 vs 18.6, P = 0.54  Bone only metastases: 70.4 vs 62, P < 0.001  Visceral metastases: 83 vs 52.7, P < 0.001
Choi <i>et al</i> [38]	245	LRT (n = 82): Surgery, RT or both  No LRT (n = 163)	LRT arm: < T4, no liver or brain metastasis, and < 5 metastatic sites	40	5-yr LRFS: 62% vs 20%, P < 0.001  5-yr OS: 73% vs 45%, P = 0.02
Gultekin <i>et al</i> [7]	227	LRT (n = 188): Surgery, RT or both  No LRT (n = 39)	LRT arm: Less T3-4 and more solitary metastases	35	5-yr OS: 56% vs 24%, P < 0.001  5-yr PFS: 27% vs 7%, P < 0.0001
Nguyen <i>et al</i> [39]	733	LRT (n = 378): Surgery, RT or both  No LRT (n = 355)	LRT arm: Younger, more T1-2, N0-1, limited M1 disease	21	5-yr OS: 21% vs 14%, P < 0.001  5-yr PFS 72% vs 46%, P < 0.001
Neuman <i>et al</i> [25]	186	Surgery (n = 69): 13% RT No surgery (n = 117)	Surgery arm: More HER2-negative, smaller tumors, more solitary metastasis	52	No difference in OS (P = 0.10)

NCDB: National Cancer Database; SEER: Surveillance, Epidemiology, and End Results, RT: Radiotherapy; LRT: Locoregional treatment; T: Tumor; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; N: Node, Gr: Grade; M: Metastasis; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; BCSS: Breast cancer-specific survival; LRFS: Local recurrence-free survival.

The prospective studies exploring the role of SBRT to metastatic sites in oligometastatic breast cancer are limited (Table 4)[5,6,9,26,30,31]. Milano *et al*[9] performed hypofractionated stereotactic radiation (50 Gy in 10 fractions) to all sites of disease in 48 breast cancer patients with 1-5 extracranial metastases. The authors observed that some patients who have only bone metastases rather than visceral metastases and with low tumor burden (volume and number of lesions) survived longer than 10 years[9]. Five- and ten-year OS rates after hypofractionated stereotactic radiation was 83% and 75%, for patients with only bone metastases vs 31% and 17%, respectively, for patients with not only bone metastases[9]. Trovo *et al*[6] in a prospective phase II trial

**Table 3 Retrospective studies investigating the role of radiotherapy as a local treatment of metastases in oligometastatic disease**

Ref.	n	Treatment	Patients	Median follow-up (mo)	Outcomes
Weykamp <i>et al</i> [28]	46	SBRT: Bone, lung, liver, adrenal gland  Median 3 frx (1-10)/28 Gy (24-60 Gy)	Inclusion criteria: breast cancer, oligometastatic ( $\leq 3$ ) or oligoprogressive (1) disease  58 lesions	21	2-yr LC, DC, PFS and OS: 89%, 44%, 17%, and 62%, respectively  Solitary metastasis: Poor prognostic factor for DC and PFS  Higher age: Poor prognostic factor for OS
Kobayashi <i>et al</i> [29]	75	Primary systemic chemotherapy: CR/PR  Surgery or RT	Inclusion criteria: breast cancer, $\leq 2$ metastatic organs, $< 5$ metastases, $< 5$ cm lesions	103	10-yr and 20-yr OS: 59.2% and 34.1%, respectively  10-yr and 20-yr RFS: 27.4%  Single organ metastasis, local treatment and shorter DFI: Better RFS
Hong <i>et al</i> [4]	361	SBRT  10 frx/50-60 Gy or 3 frx/24-48 Gy	Extracranial oligometastases ( $\leq 5$ )  Breast cancer (16%)	26.2	3-yr OS, PFS and TMC were 56%, 24%, and 72%, respectively  Primary tumor type, interval to metastasis, number of treated metastasis, and mediastinal/hilar LN, liver, or adrenal metastases: Associated with OS  All breast cancer patients: RPA class 1 (3-yr OS 75%)
Cha <i>et al</i> [40]	49	Endocrine therapy plus LRT ( $n = 33$ )  82% RT: Bone, LN  Endocrine therapy alone ( $n = 16$ )	Inclusion criteria: HR-positive, HER2-negative  Similar patient and tumor characteristics	101.6 vs 105.6	Median OS (mo): 72.3 vs 91, $P = 0.272$  Median PFS (mo): 30 vs 18, $P = 0.049$

SBRT: Stereotactic body radiation therapy; frx: Fraction, Gy: Gray, CR: Complete response; PR: Partial response; RT: Radiotherapy; LN: Lymph node; LRT: Locoregional treatment; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; LC: Local control; DC: Distant control; OS: Overall survival; PFS: Progression-free survival; DFI: Disease-free interval; TMC: Treated metastasis control; RPA: Recursive partitioning analysis.

administered SBRT (30-45 Gy in 3 fractions) or intensity-modulated RT (60 Gy in 25 fractions) to all metastatic sites in 54 oligometastatic breast cancer patients whose primary tumor was controlled. The authors reported that 2-year local control, OS, and PFS rates with a median follow-up of 30 mo were 97%, 95%, and 53%, respectively, and no  $\geq$  grade 3 toxicity was documented[6]. The first randomized phase II study in metastatic cancer is the SABR-COMET study in which 99 patients with the oligometastatic disease were randomized to receive systemic therapy plus palliative RT (8 Gy in 1 fraction or 30 Gy in 10 fractions) or systemic therapy plus SABR to all metastatic sites. Only 18% of the patients were with breast cancer in this study. There was a significant improvement in terms of 5-year OS (17.7% vs 42.3%,  $P = 0.006$ ), 4-year PFS (3.2% vs 21.6%,  $P = 0.001$ ), and local control rates (46% vs 63%,  $P = 0.039$ ) in patients treated with SABR without any significant adverse events[5]. Results of three ongoing prospective randomized studies (SABR-COMET 10, STEREO-SEIN, and NRG-BR002) are being expected to clarify the role of SBRT to all metastatic sites in oligometastatic breast cancer[32-34].

## CONCLUSION

Metastatic breast cancer includes a wide spectrum of disease ranging from oligometastatic to disseminated disease. There has been growing interest during the last 20 years in the curative treatment of oligometastatic breast cancer with the advances in systemic therapy. Aggressive local treatment of primary tumor and metastases-directed therapies may improve survival in selected patients, and should especially be suggested to young patients with limited number of metastases. The results of ongoing trials specific to breast cancer will be more helpful in the future.

**Table 4** Prospective studies exploring the role of radiotherapy to metastatic sites in oligometastatic disease including primary breast cancer

Ref.	n	Treatment	Patients	Median follow-up (mo)	Outcomes
Palma <i>et al</i> [5]	99	Palliative RT ± systemic therapy (n = 33) 1 frx/8 Gy or 10 frx/30 Gy  SABR ± systemic therapy (n = 66)  Different regimens according to tumor size and location	Inclusion criteria: 1-5 metastases, life expectancy ≥ 6 mo, controlled primary tumor  Primary breast cancer (n): 5 vs 13	51	5-yr OS: 17.7% vs 42.3%, P = 0.006 4-yr PFS 3.2% vs 21.6%, P = 0.001 LC 46% vs 63%, P = 0.039 ≥ Gr 2 toxicity: 9% vs 29%, P = 0.026 SABR: Gr 5 toxicity (n = 3)
Milano <i>et al</i> [9]	48	HSRT: ≥ 50 Gy in 10 frx	Inclusion criteria: breast cancer, 1-5 extracranial metastases, primary controlled	52	5- and 10-yr OS: Bone-only oligometastases: 83% and 75% Non-bone-only oligometastases: 31% and 17% (P = 0.002) GTV > 25 cc: Poor prognostic factor for LC
Trovo <i>et al</i> [6]	54	SBRT: 3 frx/30-45 Gy (n = 44)  IMRT: 25 frx/60 Gy (n = 10)	Inclusion criteria: breast cancer, ≤ 5 extracranial metastases, primary controlled  92 lesions	30	2-yr LC: 97% 2-yr OS: 95% 1- and 2-yr PFS: 75% and 53%, respectively No ≥ Gr 3 toxicity
Salama <i>et al</i> [26]	61	SBRT: Lung, LN, liver, bone, adrenal, soft tissue, pancreas  3 frx/24-48 Gy	Inclusion criteria: 1-5 metastatic sites, life expectancy > 3 mo  Breast cancer (11.3%)	20.9	1-yr and 2-yr OS: 81.5% and 56.7%, respectively 1-yr and 2-yr PFS: 33.3% and 22.0%, respectively
Scorsetti <i>et al</i> [31]	33	SBRT: 3-4 frx/48-75 Gy	Inclusion criteria: breast cancer, < 5 lung or liver metastases, other metastatic sites stable or responding after chemotherapy  43 lesions	24	1- and 2-yr LC: 98% and 90%, respectively 1- and 2-yr OS: 93% and 66%, respectively 1- and 2-yr PFS: 48% and 27%, respectively No grade 3-4 toxicities
Milano <i>et al</i> [30]	40	SBRT doses and fractionation was not mentioned	Inclusion criteria: breast cancer, ≤ 5 metastases	NR	4-yr OS: 59% 4-yr PFS: 38% 4-yr LC: 89% Favorable prognosis: Solitary metastasis, smaller tumor volume, bone-only disease, and stable or regressing lesions

RT: Radiotherapy; frx: Fraction; Gy: Gray; SBRT: Stereotactic body radiation therapy; HSRT: Hypofractionated stereotactic radiotherapy; IMRT: Intensity-modulated radiation therapy; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; LC: Local control; LN: Lymph node; Gr: Grade; GTV: Gross tumor volume.

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