Review Article on Loco-regional Therapy for Metastatic Breast Cancer

Radiation therapy for oligometastatic bone disease in breast cancer

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Abstract: Breast cancer (BCa) frequently metastasizes to the bone. BCa patients with oligometastatic bone diseases have much more favorable outcomes than those with metastatic bone disease. Radiation therapy (RT), especially stereotactic body radiation therapy (SBRT), is advised for the treatment of patients with oligometastatic bone disease in other primary sites. This line of treatment provided favorable outcomes in patients and resulted in only mild toxicities. A similar strategy has been suggested for treatment of BCa patients with oligometastatic bone disease. BCa, bone-only, or high radiation dose are reported to have been associated with good outcomes in RT for metastatic disease. Furthermore, based on the guidelines provided by the BCa expert panel of the German Society for Radiation Oncology and members of the Working Party of Gynecologic Oncology Breast Committee and in line of the results obtained in other primary sites, our group supports the use of high-dose RT or SBRT for the treatment of BCa patients with oligometastatic bone disease. Additionally, the use of magnetic resonance imaging (MRI) for proper target volume definition and three-dimensional (3D) treatment planning especially for lesions of the trunk are essential for the treatment planning of RT. Of note, several clinical trials have combined RT with immune checkpoint inhibitors for the treatment of BCa patients with metastatic disease. Based on this, we anticipate that combined RT and ICI may serve as a better treatment modality for BCa patients with oligometastatic bone disease.

Keywords: Bone metastasis; breast cancer (BCa); oligometastatic; radiation therapy (RT); stereotactic body radiation therapy (SBRT)

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Introduction

Bone is the most common site for metastasis in breast cancer (BCa) (1). In about 20% of the patients, tumors of the breast metastasize to the bone. Moreover, bone metastasis (BM) occurs in more than half of the cases showing distant metastases (2). Additionally, up to 70% of the patients who succumb to BCa show evidence of metastatic bone disease, post-mortem (3). BCa patients with first BM have a median survival time of about 20 months, and a 10% 5-year survival rate (4). Whereas, the 5-year survival rate for BCa patients with singular or oligometastatic bone disease is in the favorable range of 58.4–83% (5-7).

The treatment of patients with BM includes the systemic administration of antitumor and antiresorptive agents, and/or localized radiation therapy (RT), radiofrequency ablation,

Table 1 RT for oligometastatic bone disease in other primary sites

Author, year	No. of patients	Histology	RT dose and fractionation	Local control outcomes	Survival outcomes	Grade ≥3 toxicity
Patel *et al.* (11), 2019	51	Prostate	10 Gy ×3, SBRT	90% (3 years)	73% (4 years)	0
Silva *et al.* (12), 2019	20	Mixed	8–10 Gy ×3, 5–8 Gy ×5, SBRT	100% (1 year)	NR	5%
Siva *et al.* (13), 2018	20	Prostate	20 Gy ×1, SBRT	89% (2 years)	100% (2 years)	3%
Hosaka *et al.* (14), 2016	27	Mixed	37.5–60 Gy	64.3% (4 years)	56.3% (4 years)	NR
Ursino *et al.* (15), 2015	28	Mixed	24 Gy ×1, 9 Gy ×3, SBRT	69% (3 years)	71.7% (3 years)	2.5%
Owen *et al.* (16), 2014	74	Mixed	18 or 24 Gy ×1, 10 Gy ×3, SBRT	91.8% (1 year)	81.4% (1 year)	0
Thibault *et al.* (17), 2014	13	Renal cell cancer	18–24 Gy ×1, 10–12 Gy ×2, SBRT	61% (2 years)	73% (2 years)	6.6%
Muacevic *et al.* (18), 2014	40	Prostate	16.5–22 Gy ×1, SBRT	95.5% (2 years)	*	NR
Wowra *et al.* (19), 2008	102	Mixed	15–24 Gy ×1, SBRT	98% (1.25 years)	68% (1.25 years)	2.0%
Rades *et al.* (20), 2007	521	Mixed	8 Gy ×1, 3 Gy ×10, 2 Gy ×20	78% (3 years)	50% (3 years)	0

*, the 75% survival proportion was achieved at 17.5 months. RT, radiation therapy; SBRT, stereotactic body radiotherapy; NR, not reported.

and surgery. RT especially plays an important role due to the radiosensitivity of BCa cells (8). Pain, limited movements, risk of fracture, after surgical intervention, and spinal cord compression are the indications for palliative RT (9). While pain relief is generally observed within a few days after the start of RT, radiologically detectable recalcification and stabilization commence at the earliest within 6–12 weeks after termination of RT. Moreover, asymptomatic patients with favorable prognostic factors can be treated using RT (10). Furthermore, high-dose RT may provide long-term localized control from skeletal manifestations and improve the overall survival (OS) of patients with oligometastases.

Here, we have described RT for the treatment of patients with oligometastatic bone disease in other primary sites and in BCa, and the future perspectives.

RT for oligometastatic bone disease in other primary sites

Some studies have opted RT for oligometastatic bone disease in other primary sites (*Table 1*) (11-20), and 8 of these 10 studies have used stereotactic body radiation therapy (SBRT). Sixty-seven percent of Grade ≥3 toxicities were fractures requiring a surgery. Overall, they resulted in excellent outcomes with mild toxicities.

A recent SABR-COMET randomized phase II study (21) has compared the responses to SBRT (30–60 Gy in 3–4 fractions or 16–24 Gy in single fraction) and conventional RT (8 Gy in single fraction to 30 Gy in 10 fractions) in 99 patients who had a controlled primary malignancy with 1–5 metastatic lesions in mixed primary sites. Amongst these, about 33.5% account for metastases to the bone. The median OS in the conventional RT group was 28 months as compared to 41 months in the SBRT group (P=0.090; where P<0.20 designates a positive trial). Adverse events of grade 2 or worse occurred in 9% of conventional RT group compared to 29% in the SBRT group (P=0.026). Additionally, treatment-related deaths occurred in 4.5% cases in the SBRT group, while no deaths occurred in the conventional RT group.

Several studies recommend SBRT for treatment of oligometastatic bone disease (22-31).The American College of Radiology Appropriateness Criteria suggests that aggressive local therapy of oligometastatic spine disease may provide survival benefit to the patients, although additional data would be required to understand the role of highly conformal RT techniques that allow for radiation dose escalation (32). The evidence-based guidelines of The American Society for Radiation Oncology (ASTRO) do not describe the use of curative intent SBRT for treatment of

Table 2 RT for oligometastatic bone disease in BCa

Author, year	No. of patients	RT dose and fractionation	Local control outcomes	Survival outcomes	Grade ≥3 toxicity
Milano *et al.* (5), 2019	12	5 Gy ×10, SBRT	100% (5 years)	83% (5 years)	0
Miyata *et al.* (6), 2017	17	40–74 Gy, in 1.8–2 Gy fractions	85% (5 years)	73% (5 years)	5.9%
Yoo *et al.* (34), 2015	31	20–60 Gy	66.2% (5 years)	61.6% (5 years)	NR
Takemoto *et al.* (7), 2009	11	2 Gy × (20–25), 3 Gy ×10	80% (5 years)	58.4% (5 years)	NR
Rades *et al.* (20), 2007	149	8 Gy ×1, 3 Gy ×10, 2 Gy ×20	79% (3 years)	51% (3 years)	0

RT, radiation therapy; BCa, breast cancer; SBRT, stereotactic body radiotherapy; NR, not reported.

oligometastatic bone disease (33). Instead, the guidelines suggest that eligible patients with metastases to the spine be considered for available SBRT trials to clarify the role of optimal treatment approach.

RT for oligometastatic bone disease in BCa

Few studies suggest RT for treatment of patients with oligometastatic bone disease in BCa (*Table 2*) (5-7,19,34). In these studies, only a single patient presented grade 3 acute dermatitis with grade ≥3 toxicity. Overall, patients received a high radiation dose that resulted in favorable outcomes, and mild toxicities. Here, Milano *et al.* (5) reported that the 5- and 10-year OS rates after SBRT were 83% and 75%, respectively, for bone-only patients *vs.* 31% and 17%, respectively, for other patients (P=0.002). Next, Rades *et al.* (20) suggest that the outcomes were most favorable in patients with myeloma/lymphoma followed by those with BCa, and that none of the BCa patients showed progression of motor deficits. Additionally, Yoo *et al.* (34) reported that high-dose RT (≥50 Gy_{10}) and HER2-negative status were significantly associated with improved local control, and Takemoto *et al.* (7) reported that local recurrence was observed in a patient treated with 3 Gy ×10 irradiation, the lowest dose among the eleven patients.

In a prospective study by Owen *et al.* (16), 74 patients with non-spine bone oligometastases (inclusive of 8% BCa) treated with SBRT were administered 18 Gy or 24 Gy in a single fraction, or 30 Gy in 3 fractions. Of these, six patients with BCa did not present with local recurrence, although seven of 68 patients with other primary sites did. Also, the number of metastases at simulation (<5 *vs.* >5 metastases) was associated with reduced median OS post SBRT (10.8 *vs.* 6.4 months; P<0.0001). Next, in a retrospective study by Kobayashi *et al.* (35), 35 of 75 patients with oligometastatic BCa (39% bone) were treated with systemic chemotherapy plus metastasis-directed surgery or RT, and 40 patients were treated with systemic chemotherapy only. The 10- and 20-year OS rates were 82% and 53%, respectively in patients with multidisciplinary treatments *vs.* 42% and 23%, respectively in patients treated with systemic therapy alone (P=0.0063). Jacobson *et al.* (36) analyzed the number of sites of initial involvement identified in radionuclide bone scans in relation to long-term outcome in 113 BCa patients with bone as the sole initial site of metastatic disease. Median survival from time of recurrence and time of original diagnosis for the three bone scan categories was one lesion (n=47), 53 and 86 months; two lesions (n=22), 38 and 68 months; and ≥3 lesions (n=44), 22 and 58 months (P<0.0001 and P<0.005 for 1 and 2 lesions *vs.* ≥3).

Of note, none of the randomized clinical trials compares the effect of systemic chemotherapy plus RT with systemic chemotherapy alone for BCa patients with oligometastatic bone disease. However, the increased use of high-dose RT for treating oligometastatic bone disease, particularly in patients with BCa, as a "routine" option in many hospitals has made it difficult to conduct prospective randomized trials (37). The BCa expert panel of the German Society for Radiation Oncology and members of the Working Party of Gynecologic Oncology Breast Committee recommends a full dose-fractionated regimen, e.g., 2 Gy × 20–25 cycles, for RT of BCa patients with oligometastatic bone disease (8). Accordingly, by combining the results of RT for oligometastatic bone disease in other primary sites, we recommend high-dose RT or SBRT for BCa patients with oligometastatic bone disease.

Technically, the gross tumor volume (GTV) is the tumor visible in the magnetic resonance imaging (MRI) scans. In clinically suspected intradural extension, contrast-enhanced MRI is recommended to delineate the meningeal

enhancement and is included in the GTV. The clinical target volume (CTV) includes the GTV with an adequate (e.g., 1–2 cm) margin. Of note, the CTV should always include the complete vertebral body in case of vertebral body involvement. In the case of unaffected compacta, extension of the CTV beyond the compacta is discouraged (8). The planning target volume (PTV) margin differs based on factors such as the use of image-guided radiotherapy (IGRT) or not, the method of IGRT, reproducibility, and respiratory motion. Furthermore, the three-dimensional (3D) treatment planning is essential, especially for lesions of the trunk, because the treatment of oligometastatic bone disease requires high-dose RT and checking the irradiated dose and volume of adjacent normal tissue.

Future perspectives

Based on the current scenario, combined use of RT and immune checkpoint inhibitors (ICI) may enhance the antitumor immune response and produce a synergistic effect (38). The randomized double-blind international phase III PACIFIC trial (39) compared the effect of durvalumab as consolidation therapy with placebo in 713 patients with stage III locally advanced unresectable non-small cell lung cancer after treatment with platinum-based definitive chemoradiotherapy. The 24-month OS rate was 66.3% in the durvalumab group, as compared to 55.6% in the placebo group (two-sided P=0.005). Durvalumab significantly prolonged OS, as compared with placebo (stratified hazard ratio for death, 0.68; P=0.0025). Chicas-Sett *et al.* in their systematic review discussed the effect of combined RT and ipilimumab in patients with metastatic melanoma (40), where a survival benefit of eight months in favor of the RT plus ipilimumab combination was observed in comparison with the median OS of 11.4 months in the pooled analysis of phase II and III trials of ipilimumab without RT.

Furthermore, there are several ongoing and completed clinical trials combining RT and ICI in metastatic BCa patients (41). In future, the combined use of RT and ICI may serve as a promising therapeutic option against oligometastatic bone disease in BCa.

Conclusions

Based on results from several studies, the overall survival of BCa patients with oligometastatic bone disease is favorable compared to those with metastatic bone disease. Furthermore, we recommend high-dose RT or SBRT for patients with oligometastatic bone disease. The use of MRI for proper target volume definition and 3D treatment planning especially for lesions of the trunk are essential for the treatment planning of RT. Finally, we anticipate that combinatorial treatment using RT and ICI may benefit BCa patients with oligometastatic bone disease.

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Footnote

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