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Original Article

Oligometastatic breast cancer treated with hypofractionated stereotactic radiotherapy: Some patients survive longer than a decade

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ABSTRACT

Background: The clinical state of oligometastases describes metastases limited in number and extent, amenable to metastasis-directed therapy. We sought to analyze long-term outcomes and characterize potential prognostic factors, in women with breast cancer (BC) oligometastases treated with hypofractionated stereotactic radiation (HSRT) therapy on a prospective phase II protocol.

Methods: Forty-eight women with 1–5 extracranial BC oligometastases received HSRT to all radiographically apparent sites of disease. Various dose-fractionation schedules were used. Most ($n = 27$) received 10 daily fractions, typically ≥50 Gy ($n = 17$).

Results: BC patients with bone-only oligometastases (BO, $n = 12$) vs. all other patients (non-BO; $n = 36$) were significantly younger, more likely to present with oligometastases at the time of primary BC diagnosis (i.e., synchronous), and significantly more likely to have had hormone receptor-positive disease. The 5-year and 10-year overall survival (OS) rates after HSRT were 83% and 75%, respectively, for BO patients vs. 31% and 17%, respectively, for non-BO patients ($p = 0.002$). BO patients experienced a significantly ($p = 0.018$) greater freedom from widespread metastases (FFWM). Among non-BO patients, net oligometastatic GTV >25 cc (reflecting disease burden) was a significant factor for freedom from local recurrence ($p = 0.047$) and FFWM ($p = 0.028$). The number of oligometastatic lesions ($p = 0.007$) and organs ($p = 0.001$) involved were also significant factors for FFWM in non-BO patients.

Conclusions: Some patients with BC oligometastases treated with HSRT can survive >10 years. Tumor burden (volume and number of lesions) appears to impact risk of recurrence. Further research is needed to help better identify BC patients most likely to benefit from metastasis-directed radiotherapy.

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The clinical state of oligometastases was first described by Hellman and Weichselbaum in 1995 [1]. Oligometastases are metastases limited in number and extent, and potentially amenable to definitive metastasis-directed (i.e., surgical or ablative) treatment [2]. This concept arose from Dr. Hellman's theory of cancer progression existing along a spectrum [2,3], ranging from a state of limited disease with propensity to spread in an orderly, contiguous manner (postulated by Halsted) to a state of widespread disease from clinical inception (postulated by Fisher) [4].

The idea to utilize metastasis-directed therapy dates back decades [5,6]. In 1968, Rubin questioned "Are metastases curable?" in a JAMA editorial [7]; he also co-authored "Solitary Metastasis" [5], a book in which localized therapies for metastatic disease were explored. In the early 1980s, Peters, Milas and Fletcher postulated that, for select patients who also received systemic therapy to sterilize occult metastatic disease, radiotherapy to overt sites of disease could potentially be curative [8].

Systemic therapy remains the standard of care for metastatic disease. However, recent advances in radiographic and functional imaging, minimally invasive surgical and ablative techniques, radiotherapy and systemic therapies have made the hypothesis of metastasis-directed therapy for oligometastases more compelling.

There is a growing evidence supporting the use of radical irradiation for oligometastases [9,10]. The NRG BR001 phase I study affirmed, in a prospective cooperative group trial, the tolerability of stereotactic body radiotherapy (SBRT) for patients with multiple oligometastases from breast cancer (BC), prostate cancer or non-small cell lung cancer (NSCLC) [11]. From the multi-national SABR-COMET randomized phase II screening trial of 99 patients ($n = 18$ with BC, with 13 of 66 in the treatment arm) with 1–5 oligometastases (1–3 in 93% of patients), the use of stereotactic ablative body radiotherapy (SABR, synonymous with SBRT), versus standard of care therapy alone, significantly increased the median progression-free survival (PFS; 12 vs. 6 months, $p = 0.001$); the

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median overall survival (OS) difference (41 vs. 28 months, $p = 0.09$) met the study's endpoint of $p < 0.20$ [12]. These promising results prompted the investigators to amend the protocol to allow for re-evaluation after 10-years of follow-up, and to develop phase III studies for patients with 1–3 and 4–10 oligometastases.

BC represents the most common malignancy in women [13]. Among BC patients with metastatic disease, ~50% present with 1–2 metastases [14], and in one series [15], ~90% present with 4 or fewer metastases. BC is therefore potentially well-suited for metastasis-directed therapy in select patients [14,16–19]. In a retrospective study of 75 oligometastatic BC patients, treated from 1980−2010, metastasis-directed surgery or radiotherapy (in 35 patients) was associated with significantly improved survival outcomes at 10–20 years [20].

Several studies have shown that, compared to oligometastases from other primary cancers, oligometastatic BC patients have more favorable survival and/or tumor control outcomes. These include patients treated with surgical resection [21] or with ablative doses of radiotherapy [22–29], of which some studies were limited to lung metastases [21,24] or liver metastases [29]. Some studies described subgroups of favorable histologies and/or primary sites that included BC [21,25,28]. In one study, ablative radiotherapy for oligometastatic BC ($n = 17$ patients) was not more favorable than for non-BC ($n = 59$ patients) [30].

After pulmonary metastasectomy for oligometastatic BC, reported 10-year survival rates from large registry studies are on the order of 22–32% [21,31]. Favorable long-term survival outcomes after hepatic resection of oligometastatic BC have also been reported [16,32], with a 10-year survival of 23% in one study of 28 patients [33].

Long-term (10+ year) data on metastasis-directed radiotherapy for oligometastatic BC are lacking. The aforementioned study with 20+ year follow-up did not describe radiation dose, dose-fractionation, or techniques [20]. We sought to analyze 10-year outcomes of women treated with metastasis-directed stereotactic radiotherapy on a prospective phase II protocol in an effort to better understand long-term outcomes and factors that may impact these outcomes. Prior publications from our group referred to this treatment as SBRT; however given the American Society of Radiation Oncology and American College of Radiology definition of SBRT as being delivered ≤5 fractions, we favor the term hypofractionated stereotactic radiotherapy (HSRT) for this study.

Methods

Survival and tumor control outcomes in oligometastatic BC patients, enrolled on a prospective study of metastasis-directed radiotherapy, are analyzed. All patients were required to have a Karnofsky performance status score of ≥70 and 1–5 oligometastases, limited to 1–3 organs. We previously analyzed outcomes of 121 oligometastatic patients (of whom 39 were oligometastatic BC patients) after metastasis-directed radiotherapy [22]. The present study is limited to patients with extracranial oligometastases from primary BC. One oligometastatic BC patient with brain oligometastases, who was included in earlier studies [22,34–36], is excluded in this analysis. Patients treated with 'palliative intent' (radiation to selected lesions in the setting of >5 metastases), of whom 11 were analyzed in a prior study [36], are also excluded here. An additional 10 patients who enrolled from 2007 through 2011, for a total of 48 oligometastatic BC patients enrolled from 2001 to 2011, are included in the present analysis. The primary BC was controlled and/or recently treated in all patients. This study was approved by the University of Rochester Research Subjects Review Board, and reopened in 2018 for reanalysis. All patients signed informed consent prior to enrollment.

Immobilization and motion management techniques were described previously [22,34]. Stereotactic localization techniques were used in all patients. Various dose-fractionation schedules were used; the protocol described suggested 3–10 Gy per fraction dose-schedules for prescribed dose, but allowed the treating physician discretion, in order to adhere to protocol mandated normal tissue dose constraints (described previously [37] and in the supplemental material). All but 2 patients were prescribed daily fractional doses of 3–17 Gy. Most ($n = 27$) received 10 fractions, typically 50 Gy ($n = 15$) or higher ($n = 2$). Only 4 patients received SBRT using five ($n = 3$) or fewer ($n = 1$) fractions. Targeting and treatment planning techniques were described previously [22,34].

Net gross target volume (GTV) represents the sum of each lesion's GTVs based upon contoured volumes from the radiation planning CT scan. Previously resected metastases were not included in net GTV; likewise, changes in tumor volume resulting from prior systemic therapy are not accounted for. Because of various dose-fractionation schedules used, an equivalent dose in 2-Gy fractions (EQD2) was calculated, using the linear-quadratic model with an alpha–beta ratio of 10.

Patients were subgrouped into those with bone-only oligometastases ("BO") vs. those with oligometastases outside of bone ("non-BO" with or without bone oligometastases), based upon our prior analysis showing the significance of BO in oligometastatic BC patients [36], as well as bone-only metastatic BC (i.e., not specifically oligometastatic) being a favorable factor for survival [38].

Widespread metastases represent distant progression not amenable to resection or ablative therapy. Local recurrence (i.e., recurrence of treated metastasis) represents growth of any treated lesion by ≥20%, based on Response Evaluation Criteria In Solid Tumors (RECIST) criteria [39]. Freedom from widespread metastases (FFWM), freedom from local recurrence (FFLR), and OS were calculated using Kaplan–Meier's actuarial survival analyses. OS was defined from date of enrollment until death or last follow-up; FFLR and FFWM were defined from date of enrollment until death, an event, or last radiographic study. For comparison of survival and tumor control outcomes, log-rank tests were used for univariate analyses of binned variables and Cox regression was used for univariate analyses of continuous variables and for multivariate analyses. Stata version 9.2 was used for data analysis.

Results

All patients were female and all but 2 were white (one was black and another Asian). Table 1 shows additional clinicopathologic characteristics of the 48 patients treated with HSRT for extracranial oligometastatic BC. BO (vs. non-BO) was associated with significantly younger age ($p = 0.020$), greater likelihood of oligometastases presenting synchronously with primary BC ($p = 0.007$), greater likelihood of hormone receptor-positivity ($p = 0.024$), and lower likelihood (among those who received systemic therapy prior to HSRT) of having had progression of oligometastases prior to protocol enrollment ($p = 0.037$).

Table 2 summarizes survival and tumor control outcomes after HSRT, and Fig. 1 depicts OS. BO (vs. non-BO) had a significantly greater OS ($p = 0.002$) and FFWM ($p = 0.018$) on univariate analyses. With multivariate analyses of BO vs. non-BO, sum of GTVs (>25 vs. <25 cc), hormone receptor-positivity, and number of lesions (1 vs. >1), BO remained a significant factor for OS ($p = 0.026$) and FFWM ($p = 0.037$).

All surviving patients have lived at least 9.6 years. None of the 4 patients enrolled after 2009 are alive; one died from pre-existing liver disease, without progression of BC, 4 years after SBRT to a right middle lobe lung metastasis (not in the vicinity of the liver).

Table 1
Patient and treatment characteristics.

	Excluding bone-only oligometastases	Bone-only oligometastases	p value
Number of patients	36	12	
Age (years)			
Median [range]	60.0 [42.8–64.9]	43.9 [36.3–84.6]	**0.020**
Time interval (months)			
– Primary diagnosis to metastases[†]			
Synchronous (<2 months)	3 (8%)	5 (42%)	**0.007**
Metachronous	33 (92%)	7 (58%)	
– Median [range] (months)	54 [11–228]	36 [8–82]	0.13
– Metastases[†] to oligometastases[*]			
Synchronous (<2 months)	31 (86%)	12 (100%)	
Metachronous	5 (14%)	0	
– Median [range] (months)	24 [12–55]		
– Oligometastases[*] to protocol enrollment			
– Median [range] (months)	7 [1–77]	10 [1–96]	
Estrogen and/or progesterone receptor positivity	20 (56%)	11 (92%)	**0.024**
Sites involved with oligometastatic disease			Not analyzed
– Lung	15 (42%)	NA	
– Thoracic lymph nodes	11 (31%)	NA	
– Liver	14 (39%)	NA	
– Pelvic or abdominal lymph nodes	3 (8%)	NA	
– Adrenal	2 (6%)	NA	
– Bone	2 (6%)	12 (100%)	
Number of oligometastases treated			0.41
– 1	12 (33%)	7 (58%)	0.13 (1 vs.2–5)
– 2	12 (33%)	3 (25%)	
– 3	5 (14%)	2 (16%)	
– 4	3 (8%)	0	
– 5	4 (11%)	0	
Number of involved organs			
– 1	26 (72%)	12 (100%)	Not analyzed
– 2	9 (25%)	NA	
– 3	1 (3%)	NA	
Sum of GTVs			
Median [range]	29.0 [1.3–402] cc	20.9 [4.8–79.4] cc	0.10
<25 cc	17 (47%)	6 (50%)	0.87
Dose in EQD2			
Median [range] (Gy)	62.5 [39.3–83.3]	57.3 [38.3–70]	0.54
Systemic therapy for oligometastases prior to HSRT			
– Any	32 (89%)	12 (100%)	0.23
– Chemotherapy and/or antibody therapy	23 (64%)	7 (58%)	
– Hormonal therapy	16 (44%)	11 (92%)	
Treated lesion response to systemic therapy			
– stable	4 (11%)	4 (33%)	
– partial response	7 (19%)	1 (8%)	
– progression	14 (39%)	1 (8%)	**0.037**
– not applicable (no systemic therapy used)	4 (11%)	0	
– unable to assess[**]	7 (19%)	6 (50%)	
Systemic therapy after HSRT (before potentially developing widespread disease)			
– Any	26 (72%)	11 (92%)	0.17
– Chemotherapy and/or antibody therapy †	19 (53%)	4 (33%)	
– Hormonal therapy	17 (47%)	10 (83%)	
Systemic therapy for widespread disease			Not analyzed
– Any	16 (44%)	6 (50%)	
– Chemotherapy and/or antibody therapy	15 (42%)	6 (50%)	
– Hormonal therapy	8 (22%)	6 (50%)	
– None	3 (8%)	0	
– NA (i.e. no widespread disease)	7 (19%)	6 (50%)	
– Unknown	10 (28%)	0	

EQD2 = equivalent dose in 2-Gy fractions using linear quadratic model with an alpha–beta ratio of 10; GTV = gross target volume; HSRT = hypofractionated stereotactic radiotherapy, NA = not applicable

Oligometastases

[*]oligometastases treated on protocol.

Metastases [†]any metastatic disease. Five patients had metastases diagnosed and treated prior to developing the oligometastases treated on protocol.

[**]If systemic therapy started within 3 months before HSRT and/or before new imaging was obtained, response could not be assessed.

[†]Among women who did not have progression of oligometastatic disease prior to metastasis-directed radiotherapy, chemotherapy and/or antibody therapy agents given after radiotherapy included vinorelbine, capecitabine, paclitaxel protein-bound, and trastuzumab. Among women whose oligometastases progressed prior to metastasis-directed radiotherapy, systemic agents given after radiotherapy included vinorelbine, gemcitabine, capecitabine, carboplatin and taxotere, trastuzumab and lapatinib. Bisphosphonates were used in most patients with bone metastases during the course of their therapy, but were not considered ‘‘chemotherapy” in these tables.

Table 2
Patient survival and tumor control outcomes.

	Excluding bone-only oligometastases	Bone-only oligometastases	Univariate p value	Multivariate p value*
Overall survival			**0.002**	**0.026**
– Median [range] (years)	3.2 [0.5–17.9]	not reached [2.9–16.8]		
– 5-year	31%	83%		
– 10-year	17%	75%		
Freedom from LR of treated lesion(s)			0.076	0.052
– 2-year, 5-year and 10-year‡	73%	100%		
Freedom from widespread metastases			**0.018**	**0.037**
– 2-year	42%	75%		
– 5-year	30%	67%		
– 10-year	15%	67%		
Repeat hypofractionated metastasis-directed radiotherapy				
– For local recurrence	2 (6%)†	1 (8%)	Not analyzed	Not analyzed
– Median [range] (years)	1.0 (0.8–1.2)	13.8		
– 2nd course for new oligometastases	11 (31%)	4 (33%)		
– Median [range] (years)	0.8 [0.6–11.6]	6.3 [5.0–9.8]		
– ≥3 courses for new oligometastases	5 (14%)	2 (17%)		

‡ No local recurrences (LR) between 2 and 10 years; 1 LR recurrence at 14.1 years in a patient treated for bone-only oligometastases; 1 LR at 10.4 years in a patient treated for an oligometastatic mediastinal lymph node.
† One other patient underwent resection for LR.
* Cox regression including variables of bone-only vs. non-bone-only oligometastases, sum of GTVs (>25 cc vs. <25 cc), estrogen and/or progesterone receptor positivity, and number of lesions (1 vs. >1).

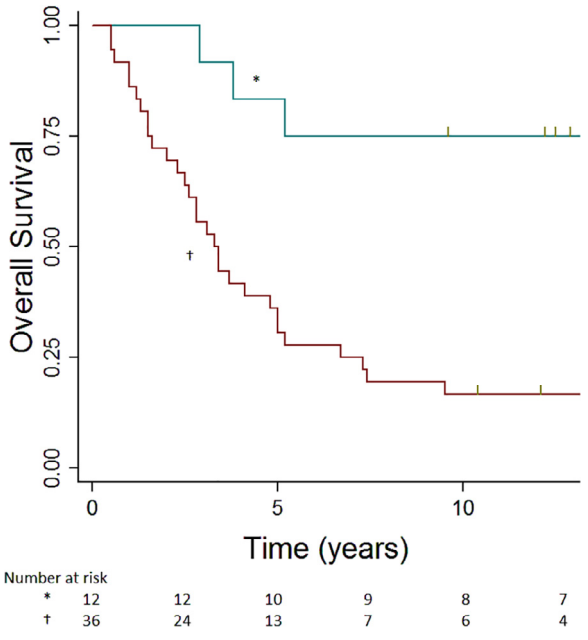

Fig. 1. Kaplan–Meier's curve of overall survival after hypofractionated stereotactic radiotherapy among those with bone-only oligometastases (*) vs. all other oligometastatic (†) patients with breast cancer.

For OS, median follow-up is 4.4 years, with 14 patients alive at 9.6–17.9 (median 14.3) years. For FFWM and FFLR, median follow-up (from enrollment to last imaging) is 3.5 years for all patients, and 12.4 years among those alive at last follow-up.

Nine of 12 BO patients (75%) have survived ≥9.6 years. Among these 9 patients, 1 died from bone and liver metastases at >16 years from enrollment, another is alive with bone-only widespread metastases, controlled with palliative radiotherapy and systemic therapy, and another is alive with thyroid and adrenal metastases that developed 12 years after HSRT for spine metastases. Four others (all still alive) have undergone SBRT/HSRT for new oligometastases (2 with extraosseous oligometastases) after their initial course. Among 3 other BO patients that have since died (at 0.9–5.2 years), all developed extra-osseous widespread brain ($n = 2$), liver ($n = 2$) and/or pleura ($n = 1$) metastases.

Six of 36 (17%) non-BO patients have survived ≥10 years. Among these 6 patients, 1 is lost to follow-up (though known to be alive) and 1 is alive with widespread metastases controlled with systemic therapy. Initial metastatic sites for these 6 patients included lung/thoracic nodes ($n = 5$, one of whom also had a bone metastasis) and liver ($n = 1$). Three had a single oligometastasis. Two underwent additional courses of HSRT for new oligometastases. Four of the 6 had hormone receptor-positive disease.

The supplemental tables present univariate analyses for potential prognostic factors affecting OS, FFWM and FFLR. For BO patients, hormone receptor-positivity ($p = 0.0009$), and response to systemic therapy prior to HSRT ($p = 0.025$), were significantly favorable factors for OS and FFWM; one (vs. >1) oligometastatic lesion was also significantly favorable for OS ($p = 0.02$) but not FFWM. The analyses on factors potentially impacting FFLR in BO patients were limited due to there being only 1 event in 12 patients. For non-BO patients, no analyzed factor other than development of widespread metastases was significantly associated with OS. One (vs. >1) oligometastasis ($p = 0.007$), one (vs. >1) organ involved ($p = 0.001$) and higher EQD2 ($p = 0.048$) were significantly favorable factors for FFWM. Net GTV (>25 vs. <25 cc) was a significant factor for FFLR ($p = 0.047$) and FFWM ($p = 0.028$), and borderline significant for OS ($p = 0.069$). No other analyzed factor (including EQD2) significantly predicted FFLR.

Discussion

To our knowledge, this study represents the longest follow-up after HSRT for oligometastatic BC. Significant findings include a markedly, and significantly, greater OS in BO vs. non-BO patients. Among BO patients, those who died during the follow-up interval (4 patients) had ultimately developed extraosseous widespread metastases. Hormone receptor-positivity, which was more common (92% vs. 56%, $p = 0.024$) in BO, was significantly associated with more favorable OS and FFWM in BO patients, albeit with only 1 hormone receptor-negative BO patient. Synchronous vs. metachronous development of oligometastases (relative to the primary tumor), with the latter possibly suggesting more indolent disease,

was not a significant factor for any outcome in this study, as it was in another study that included non-BC patients [40].

For both BO and non-BO, local recurrence was not significantly correlated with OS, likely reflecting potential salvage options of resection or re-irradiation. Unsurprisingly, development of widespread metastases significantly impacted OS in non-BO patients; a similar relationship was not observed in BO patients, likely due to a small cohort with few events. Among non-BO patients, the numbers of oligometastases (1 vs. >1) and organs involved (1 vs. >1), which are interdependent, were significantly associated with FFWM; this association did not translate into significant relationships of lesion or organ number with OS, perhaps due to salvage systemic therapy. For non-BO patients, GTV >25 cc was a significantly adverse factor for FFLR and FFWM (and borderline significant for OS), also suggestive that disease burden is a prognostic factor. GTV analyzed a continuous variable was not a significant factor, likely due to the wide range in GTV.

Several other studies have also examined outcomes and prognostic factors in patients undergoing metastasis-directed radiotherapy for oligometastatic BC. In a Korean study, 50 women with 1–5 metachronous, extracranial oligometastatic BC (all with bony sites; $n = 7$ with additional extraosseous sites) were treated with conventional radiation; 5-year local control (LC) and 3-year FFWM rates were 66.1% and 36.8%, respectively [41]. A biologically effective dose >50 Gy was associated with significantly greater LC and OS on univariate, but not multivariate, analyses. Hormone receptor-positivity and single (vs. > 1) metastasis were associated with significantly improved OS on univariate and multivariate analyses. Age (<40 vs. ≥40), Her2 status, and systemic therapy were not significant factors.

From an observational study of 33 female oligometastatic BC patients with 1–3 liver or lung oligometastases, treated with SBRT (48–75 Gy in 3–4 fractions), with 2-years of median follow-up, 2-year PFS, LC and OS were 27% and 66%, respectively [42]. A longer interval from initial diagnosis to metastases, hormone receptor-positivity and systemic therapy administration after SBRT were favorable factors for OS on univariate, but not multivariate, analyses. Site of metastatic disease (liver vs. lung) did not influence LC, OS or PFS.

In a multicenter, phase II, Italian study of 54 female oligometastatic BC patients with ≤5 oligometastatic sites (92 lesions, including 60 bone lesions), patients received SBRT (30–45 Gy in 3 fractions) or conventionally fractionated (60 Gy in 25 fractions) intensity-modulated radiotherapy (IMRT) [43]. After a median follow-up of 2.5 years, 2-year PFS, LC and OS were 75%, 97% and 95%, respectively. Age (<55 vs. ≥55 years), synchronous vs. metachronous presentation, estrogen receptor status, Her2 status and number of lesions (1 vs. >1) were not significant factors for relapse; tumor burden and metastatic site were not analyzed, nor were potential prognostic factors for OS. One vs. >1 metastatic sites was prognostic for OS and metastasis-PFS in a series of oligometastatic BC patients for whom the use of metastasis-directed therapy was not described (and presumably not utilized) [44].

Many studies have examined outcomes and prognostic factors in patients undergoing metastasis-directed surgery for oligometastatic BC. From a systematic review of metastasectomy of liver or lung metastases from BC, commonly reported favorable prognostic factors include fewer metastatic lesions, hormone receptor-positivity, longer disease-free survival, and younger age [45]. A solitary lesion (vs. multiple lesions) was favorable (though not significant) in the International Registry of Lung Metastases analysis; a longer disease-free interval was a highly significant factor in that study ($p = 0.00001$) [31]. Response to systemic therapy has been reported as a favorable prognostic factor after BC metastasectomy in two studies [20,46], though not another [47]. Few studies have analyzed disease bulk as a prognostic factor for oligometastatic BC. Tumor size was a significantly adverse factor for survival outcomes in some studies of BC patients undergoing liver [46,48,49] or lung [50] metastasectomy.

One limitation of the current study is the variable dose-fractionation schedules used (see supplemental material). Converting prescribed doses to EQD2 corrects for variability to some extent, though the linear-quadratic model relies on assumptions that may not apply to HSRT [37,51]. As described previously [22], fractional doses in excess of 8 Gy were just beginning to be investigated when this study began, and thus the physicians treating patients on this study opted to be somewhat conservative (relative to SBRT dose-fractionation schedules commonly used today). Less aggressive dose-fractionation is seemingly effective though (as also reported for NSCLC patients) [52]. Another study limitation is that tumor grade and molecular subtypes were not analyzed; Her2 status was not captured in most patients, particularly those enrolled in earlier years. Additionally, specific genetic factors may predict for likelihood of widespread metastases [53,54], survival after radiotherapy for oligometastases [23] and/or radiosensitivity [55]; immunologic and/or inflammatory markers may also predict outcomes [56–58]. These factors were not considered either. Also, the wide variety in timing of systemic therapy (e.g., before HSRT, after HSRT, and/or after developing widespread metastases) and agents used preclude meaningful analysis of the impact of systemic therapy on outcomes.

The NRG BR002 study is randomizing oligometastatic BC patients with ≤4 metastases (stratified by 1 vs. 2–4 metastases, hormone receptor status, Her2 status and use of standard 1st line therapy) to standard of care systemic therapy with or without upfront SBRT or resection of all metastases (NCT02364557). Notably, a possible PFS benefit may not translate into an OS benefit in this study, since patients randomized to not receive metastasis-directed therapy can receive that treatment after disease progression, and/or can receive upfront palliative radiotherapy for symptomatic metastases (which may provide some LC benefit). Interestingly, the updated (ASTRO 2018) results from a multicenter randomized study of local consolidative therapy vs. standard of care for oligometastatic NSCLC demonstrated a PFS and OS benefit, despite possible cross-over to treatment at the time of progression; notably, 94% of study patients presented with synchronous metastases, and the primary site was therefore untreated in those patients randomized to the control arm (unlike NRG BR002, and this study, requiring controlled primary cancers) [59].

In summary, while relatively few patients in this study have survived >10 years, it is remarkable that some metastatic BC patients, particularly those with non-osseous metastases, have survived for such a long duration. Further research is needed to help ascertain if metastasis-directed radiotherapy affords a survival benefit in oligometastatic BC, and to identify patients most likely to benefit from this treatment. Pending results from NRG BR002 and other ongoing prospective trials [60], pooled analyses and systematic reviews [61] may provide additional insight into outcomes after SBRT/HSRT for oligometastatic BC.

Conflict of interest.

MM reports Royalites from UpTo Date. PO reports research grants from DiaCarta, ownership interests (including patents) and consultant/advisory baord member for Entrinsic Health, DiaCarta and Eva Pharmaceuticals.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.022.

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