



Oligometastatic breast cancer: where are we now and where are we headed? – a narrative review

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Abstract: Metastatic breast cancer has traditionally been considered incurable, with treatments focused on systemic therapies and palliative local treatment. However, evidence is emerging that in some patients with limited metastatic disease, or “oligometastatic disease,” often defined as five or fewer metastases diagnosed on imaging, aggressive metastasis-directed therapy (MDT) with surgery and/or hypofractionated image-guided radiation therapy (HIGRT) improves outcomes and may even be curative. This practice is becoming more common as evidence has grown to support the approach and as technology has made it more feasible. Treatment of certain oligometastatic breast cancers in particular (i.e., hormone receptor positive and bone-only metastases) may be especially useful given the long natural history of the disease in some of these patients. Recently, high quality data supporting ablative MDT in patients with oligometastatic disease has emerged from randomized trials for specific sites such as non-small cell lung cancer and prostate cancer, as well as from histology agnostic studies (i.e., SABR-COMET). However, randomized data in breast cancer specifically is currently lacking. Retrospective series and subgroup analysis from prospective trials have demonstrated improved outcomes with MDT for oligometastatic breast cancer. The ongoing phase II/III NRG BR002 trial seeks to provide the first randomized data to determine whether MDT in oligometastatic breast cancer improves outcomes. This may be especially important as improved systemic therapies such as targeted agents and immunotherapy prolong the disease course. Alternatively, if improved systemic therapies render patients disease free, MDT may not be necessary and only adds toxicity. However, MDT may also provide non-curative benefits for patients such as palliation of symptoms and extended time off systemic therapy. For now, aggressive MDT for certain favorable subgroups of oligometastatic breast cancer such as those with few metastases, hormone positive disease, and/or bone-only metastases is reasonable and may improve outcomes. We eagerly anticipate the results of NRG BR002 to further clarify the role of ablative therapy to all sites of disease in these patients.

Keywords: Radiofrequency ablation (RFA); liver resection; stereotactic ablative radiotherapy (SABR); trans-arterial chemotherapy (TACE); stereotactic body radiation therapy (SBRT); hypofractionated image-guided radiation therapy (HIGRT); oligometastases

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Introduction

Metastatic cancer has long been considered incurable, with treatment historically focused on systemic therapy to extend life and local therapy for palliation of

symptoms (1). However, there has been growing interest in more aggressive metastasis-directed therapies as a clinically significant portion of patients (~25%) with limited metastases treated with curative intent have long disease-

free survival (2-4). A recent international survey of more than 1,000 radiation oncologists found that more than 60% of respondents use ablative radiation therapy to treat patients with a limited number of metastases (5), with a similar use of surgical metastasectomy (6).

Despite the increasing adoption of aggressive metastasis-directed therapy (MDT), the topic warrants further discussion in a new era of recently published high quality studies both histology agnostic such as the recently updated SABR-COMET trial (7,8), and disease specific trials in colorectal cancer (9), non-small cell lung cancer (NSCLC) (10-12), prostate cancer (13,14), and the ongoing phase II/III study, NRG BR002, randomizing patients with locally controlled four or fewer breast cancer metastases to standard systemic therapy with or without ablative metastasis-directed radiotherapy or surgery (15).

Additionally, in the context of new systemic therapies, in particular targeted therapies (16-20) and immunotherapy (21,22), with the ability to destroy micrometastases and extend survival, metastasis-directed therapies for patients with limited metastatic disease may become more relevant. Alternatively, should the systemic therapies develop to a point where they render patients disease free, the addition of MDT would be moot, and only add to the risk of side effects. In this review, we will discuss the current understanding of oligometastatic disease, treatment of oligometastases, recent high-quality evidence supporting MDT in general and for breast cancer specifically, and considerations in the context of new systemic therapies. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-1128>).

What is the oligometastatic state?

The oligometastatic state was first described by Hellman and Weichselbaum based on the spectrum theory of cancer spread (23). They postulated that metastatic disease occurs on a spectrum, including a clinically distinct, intermediate stage between locoregionally confined disease and widespread distant metastases. In this intermediate state, the disease may have a more indolent biology compared to later in the metastatic cascade (24). Given this, they hypothesized that treatment of all known cancer, both primary tumors and metastases, could lead to long disease-free intervals and potentially even cure.

The term oligometastasis means “few”—from the Greek “oligos”—metastases, however, an exact number of lesions is rarely defined. Most studies have limited inclusion to

patients with five or fewer metastases (3), although some have included patients with up to eight (25). These criteria are based on imaging and may evolve with continued adoption of more sensitive imaging techniques such as PET/CT. The European Organization for Research and Treatment of Cancer (EORTC) and European Society for Radiotherapy and Oncology (ESTRO) have published recommendations for imaging-based diagnosis of oligometastatic disease (26-28), and together with the American Society for Radiation Oncology (ASTRO), ASTRO-ESTRO is currently working to establish a consensus definition.

While there is not yet a consensus definition for oligometastases, additional terms have been coined to further describe temporal patterns of cancer spread. The terms “de novo oligometastases,” or “synchronous oligometastases,” describe limited metastatic disease at the time of the initial cancer diagnosis and includes an untreated primary tumor in addition to limited metastases. The phrase “induced oligometastases” describes patients with widely metastatic disease in which most, but not all, metastases respond to systemic therapy, with a subsequent few remaining metastases (24). “Oligorecurrence” describes patients who develop limited metastases after initial definitive treatment (29). Finally, “oligoprogression” describes patients receiving systemic therapy who initially demonstrate response of all metastases to systemic therapy and subsequently experience progression in a limited number of disease sites while the rest remain controlled. It has been hypothesized that oligoprogression occurs when a limited number of tumor clonogens develop mutations that result in resistance to systemic therapy while the majority of metastases remain susceptible and controlled (30,31).

Are oligometastases common in breast cancer?

While evidence supporting the oligometastatic state was sparse when Hellman and Weichselbaum first proposed their theory, since then numerous studies have demonstrated oligometastases to be fairly common. Among patients with metastatic breast cancer enrolled on major phase II and phase III clinical trials of systemic therapies, approximately 50% present with two or fewer clinically detected metastases (32-37). Similar rates of oligometastases are seen in patients with NSCLC, melanoma, prostate cancer, and colorectal cancer (38-41).

Additionally, patients with oligometastatic breast cancer have been shown to have better outcomes than patients with widespread metastases. Data from the 1980s

demonstrated that among patients with metastatic breast cancer, the presence of five or fewer metastases was an independent predictor of survival (42). More recent data has shown that patients with early-stage breast cancer who progressed with five or fewer metastases have improved five-year (59.6% *vs.* 11.6%) and median survival (107.7 *vs.* 22 months; $P=0.001$) compared to patients with more than five metastases (43). Similarly, studies have shown improved outcomes for patients with oligometastatic prostate cancer and NSCLC compared to patients with widespread disease (38,39,44). Taken together, it is clear that oligometastatic disease, including breast cancer, is relatively common and has meaningful clinical significance.

How are oligometastases treated?

Surgery

MDT for oligometastases was first described in surgical literature. Large series have examined outcomes after resection of lung (45), liver (46), adrenal (47), and brain (48) metastases and demonstrated better-than-expected long-term disease control and survival for select patients. One retrospective series of 467 patients with metastatic breast cancer with lung metastases treated with metastasectomy demonstrated improved median survival (37 *vs.* 25 months) and five-year survival (38% *vs.* 18%) for patients receiving complete versus incomplete resection ($P=0.0009$) (49). Another retrospective series of patients undergoing liver resection for metastatic breast cancer demonstrated improved overall survival (OS) for patients with preoperative disease response or stabilization with systemic therapy compared to patients with preoperative disease progression (80 *vs.* 30 months, $P<0.001$) (50). Additional studies have reported favorable outcomes of breast cancer patients undergoing resection of brain (48,51,52) and bone (53) metastases as well. While still controversial, in the setting of these data rates of metastasectomy have been increasing across all cancer sites in recent years (6).

Radiation therapy

In addition to surgery, radiation therapy has been used to treat oligometastatic disease. The most common technique employed is often referred to as stereotactic body radiation therapy (SBRT), stereotactic ablative radiation therapy (SABR), or, perhaps more appropriately, hypofractionated image-guided radiation therapy (HIGRT). This technique utilizes high doses per fraction of highly

conformal radiation therapy with steep dose gradients to ablate targeted lesions while sparing normal tissue (54). Numerous studies have demonstrated high treated metastasis control rates with acceptable toxicities for lung (55), liver (56), adrenal (57), and multi-site HIGRT (58,59). Long-term results were recently published for 48 patients with oligometastatic breast cancer treated with HIGRT as a subset of patients enrolled on two prospective trials investigating HIGRT for oligometastatic disease of various primary tumors (URCC 8700 and URCC 9700) (60). In this subset of breast cancer patients, 5- and 10-year overall survival was 83% and 75%, respectively, for patients with bone-only oligometastases, while patients with non-bone oligometastases had 5- and 10-year OS of 31% and 17%, respectively. In light of this emerging evidence, the use of HIGRT to treat oligometastases has increased over time. A recent international survey of over 1,000 radiation oncologists reported over 60% of practitioners are treating oligometastases with HIGRT, and of those who are not currently doing so, 59% plan to start (5).

Is oligometastatic breast cancer unique?

The long natural history of certain metastatic breast cancers, particularly those with hormone receptor positive disease and bone-only metastases, seemingly make them ideal for treatment of all oligometastases with local therapy, as extended progression-free and overall survival may best be demonstrated in the setting of slow disease progression such as in this patient population. One histology agnostic study of 361 patients with extracranial oligometastatic cancers treated with HIGRT from multiple prospective clinical trials sought to identify prognostic pretreatment factors in order to identify which patients may benefit most (61). Median OS was 47.1 months overall, and on univariate analysis patients with breast cancer had significantly longer OS compared to patients with colorectal, other gastrointestinal, NSCLC, sarcoma, and other primary tumor types. On multivariate analysis using Cox proportional hazards models, this OS difference was sustained for breast cancer compared to all but colorectal cancers. The study also used a recursive partitioning analysis (RPA) to identify prognostic classes for overall survival, and this grouped breast, kidney, and prostate cancer into a distinct group from other primary tumor types, with 3-year OS of 75% for these patients. RPA was also able to group patients with disease from these three primary sites based on progression-free survival (PFS), demonstrating 3-year PFS of 44% for this group compared

to 17% for other primary sites. Similarly, Wong *et al.* analyzed prognostic factors in 61 patients treated with oligometastasis-directed HIGRT on a dose-escalation trial (62). They found that patients with breast cancer compared to non-breast cancer had improved OS (median, two-year, and five-year OS of 4.3 years, 100%, and 50%, respectively, *vs.* 2 years, 52%, and 29%, respectively; $P=0.026$) and PFS (median, two-year, and five-year PFS of 2 years, 57%, and 29%, respectively, versus 4.7 months, 18%, and 10%, respectively; $P=0.054$). Interestingly, they also conducted an exploratory analysis in 17 patients that found primary tumor expression levels of three microRNAs (miR-23b, miR-44a, and miR-449b) predicted survival.

Molecular markers such as these may help identify which patients are most likely to benefit from MDT, and in particular hormone receptor status may be particularly important in oligometastatic breast cancer. The aforementioned retrospective study from MD Anderson of 86 patients with metastatic breast cancer who underwent resection of liver metastases found that patients with estrogen receptor (ER) and/or progesterone receptor (PR) positive disease had improved OS compared to patients with ER-/PR- disease (median 76.8 versus 28.3 months; $P<0.001$) (50). On multivariate analysis, ER- status was associated with worse overall survival [hazard ratio (HR) 3.3, 95% confidence interval (CI) 1.4-8.2; $P=0.009$]. Similarly, a study of 50 patients with extracranial oligometastatic breast cancer treated with metastasis-directed radiation therapy found worse OS for hormone receptor negative patients (HR 7.558, $P=0.001$), although notably not all of these patients received treatment to all known sites of disease (63). Among patients with oligometastatic breast cancer treated with SBRT on 2 prospective trials at the University of Rochester, ER and/or PR positivity was associated with both improved OS ($P=0.0009$) and freedom from widespread metastases ($P=0.0009$) in patients with bone-only metastases but not in patients with non-bone metastases (64). Improved outcomes for hormone receptor positive disease are likely due to a combination of more indolent disease biology and administration of hormonal therapy. In the setting of anti-HER2 therapies, HER2 status may also be an important prognostic factor in oligometastatic breast cancer treated with MDT, although to our knowledge no studies have specifically evaluated this.

What is the level 1 evidence for MDT of oligometastatic patients?

For years, evidence for MDT included only retrospective

data and small prospective series. However, large randomized trials have recently been published supporting definitive treatment of oligometastatic disease with demonstrated improvements in progression-free and overall survival, as well as decreased development of new metastases (Table 1).

Although difficult to complete, these disease specific trials will need to continue to identify the correct timing, if any, of MDT within a given disease. This is critically important for breast cancer given the long natural history of the disease in some patients and evolving systemic therapies that may alter if or when metastasis-directed therapies are administered.

A multicenter, randomized, phase II trial of patients with metastatic NSCLC with three or fewer metastases and no progression at three or more months after front-line systemic therapy randomized patients to local consolidative therapy (LCT: radiotherapy or surgery) to all active disease sites (primary and metastatic tumors) or to maintenance therapy/observation (MT/O) (10). Radiotherapy with SBRT, HIGRT, and concurrent chemoradiotherapy were allowed, per physician discretion. The trial was closed early after 49 patients enrolled because of a significant PFS benefit in the LCT arm. At long-term median follow-up of 38.8 months, patients treated with LCT compared to MT/O had significantly greater PFS (median 14.2 *vs.* 4.4 months, $P=0.022$) and OS (median 41.2 *vs.* 17.0 months; $P=0.017$). Interestingly, this trial also demonstrated a trend towards reduction in time to appearance of new metastases in the LCT arm (14.2 *vs.* 6.0 months, $P=0.11$), suggesting a possible systemic benefit to LCT (11), consistent with analyses demonstrating metastases themselves are the source of further metastatic spread (65). Similarly, a phase II trial from UT Southwestern randomized patients with limited metastatic NSCLC (primary plus up to five metastatic sites) to maintenance chemotherapy alone or HIGRT followed by maintenance chemotherapy (12). After 29 patients enrolled with a median follow-up of 9.6 months, the trial was stopped to accrual early after an interim analysis demonstrated significantly improved PFS in the HIGRT arm (9.7 *vs.* 3.5 months, $P=0.01$). Grade 3 or greater toxicities were similar in both groups, with 4 instances likely treatment related in the HIGRT-plus-maintenance arm and 3 instances likely treatment related in the maintenance chemotherapy alone arm.

Additionally, EORTC 40004 was a randomized phase II trial of 119 patients with fewer than 10 unresectable colorectal liver metastases and no extrahepatic sites of disease. Patients were randomized to receive systemic

Table 1 Randomized trials of metastasis-directed therapy (MDT) for patients with oligometastatic disease

Study	Histology [%]	No. Patients	No. metastases		Median follow-up	MDT techniques used	RT dose (Gy)	RT No. fractions	PFS (median), month		OS (median), month		Grade 3+ toxicity (%)
			Eligible	Included					MDT arm	Control arm	MDT arm	Control arm	
SABR-COMET (7)	Breast [18]; lung [18]; prostate [16]; other [29]	99	1-5	1: 42 (42%); 2: 32 (32%); 3: 18 (18%); 4: 4 (4%); 5: 3 (3%)	25 months	HIGRT	16-60	1-8	12	6	41	28	N/A G2+; 3 (9%) 19 (29%)
MDACC (11)	NSCLC	49	0-3	0-1: 32 (65%); 2-3: 17 (35%)	38.8 months	Surgery and/or HIGRT	15-70	1-33	14.2	4.4	41.2	17	5 (20%) 2 (8%)
UTSW (12)	NSCLC	29	1-6	1: 6 (21%); 2: 14 (48%); 3: 8 (28%); 4: 1 (3%); 5-6: 0 (0%)	9.6 months	HIGRT	21-45	1-15	9.7	3.5	Not reached	17	4 (29%) 3 (20%)
EORTC 40004 (9)	CRC	119	1-9	1-2: 32 (27%); 3-4: 32 (27%); 5-6: 28 (24%); 7-9: 27 (23%)	9.7 years	RFA ± resection	N/A	N/A	16.8	9.9	45.6	40.5	51 (total, not by pt) not by pt)
STOMP (13)	Prostate	62	1-3	1: 27 (44%); 2: 16 (26%); 3: 19 (31%)	3 years	Surgery and/or HIGRT	30	3	ADT-free survival, median: 17	ADT-free survival, median: 13	N/A	N/A	0 0
ORIOLE (14)	Prostate	54	1-3	N/A	18.8 months	HIGRT	19.5-48	3-5	Not reached	5.8	N/A	N/A	0 0

RT, radiation therapy; PFS, progression-free survival; OS, overall survival; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; HIGRT, hypofractionated image-guided radiation therapy; RFA, radiofrequency ablation; MDACC, MD Anderson Cancer Center; UTSW, University of Texas Southwestern.

therapy alone or systemic therapy plus aggressive local treatment with radiofrequency ablation (RFA) with or without resection. At median follow-up of 9.7 years, patients in the combined modality arm had significantly increased OS compared to the systemic therapy arm (median 45.6 *vs.* 40.5 months, HR 0.58, 95% CI 0.38–0.88; $P=0.01$) (9).

Next, the STOMP study published in 2018 was a multicenter, randomized, phase II trial of patients with biochemically recurrent prostate cancer after definitive treatment with three or fewer detectable extracranial metastases. Patients were randomized to either surveillance or MDT of all known sites of disease. At median follow-up of three years, the primary end point of androgen deprivation therapy (ADT)-free survival was greater for the treatment group (median 21 *vs.* 13 months, HR 0.60, 80% CI, 0.40–0.90, $P=0.11$) (13). Similarly, the recent ORIOLE phase II multicenter trial randomized 54 men with recurrent hormone-sensitive prostate cancer and one to three detectable metastases to HIGRT or observation. The primary outcome of progression at six months was significantly improved for patients receiving HIGRT (19% *vs.* 61%, $P=0.005$). No grade three or greater toxicities were observed (14).

Additionally, the SABR-COMET trial was an international, randomized, phase II study of 99 patients with a controlled primary tumor and one to five metastases randomized to either palliative standard of care treatments alone or standard of care plus SABR to all metastatic lesions. While this trial allowed for up to five metastases, only seven patients (7%) had more than three, and the median number was two. At median follow-up of over two years, median OS was greater in the SABR group compared to the control (41 *vs.* 28 months, HR 0.57, 95% CI, 0.30–1.10, $P=0.09$). Note, this study used a two-sided alpha of 0.2, where $P<0.20$ demonstrates a treatment worth additional investigation. Three (4.5%) of 66 patients in the SABR arm had treatment-related death (7). Notably, this trial has been criticized for imbalance in primary disease sites between the two groups: the SABR group included more breast and prostate cancers (20% and 21%, respectively) compared to the control group (15% and 6%, respectively), which may bias results as these cancers often have more indolent biology and prolonged natural histories (66).

Lastly, the long-awaited NRG BR001 trial of HIGRT for oligometastases has completed accrual but results have not yet been published. This phase I trial included patients with good performance status with four or fewer metastases amenable to HIGRT from breast, lung, or prostate primaries (67). Thirty-six patients were treated with HIGRT

to all known sites of disease and are eligible for analysis. This trial aims to establish the safety of various HIGRT dose schedules in patients with multiple metastases, and accrual has completed and results have been presented in conference proceedings. Given favorable results, treatment of similar patients has since been expanded into the ongoing randomized trials NRG BR002 for oligometastatic breast cancer and LU002 for oligometastatic lung cancer (68).

What is the evidence in breast cancer?

Over the last two decades, a growing body of non-randomized data has emerged supporting the use of MDT for oligometastatic breast cancer (Table 2).

As discussed above, retrospective surgical series have demonstrated improved survival in patients with oligometastatic breast cancer treated with metastasectomy for lung and liver metastases, including improved outcomes for patients with hormone receptor positive disease (49,50). Additionally, Trovo *et al.* conducted a prospective phase II multicenter trial in Italy of 54 patients with oligometastatic breast cancer (\leq five extracranial metastases) treated with HIGRT (30–45 Gy in 3 fractions) or intensity modulated radiotherapy (IMRT, 60 Gy in 25 fractions) to all known sites of disease. At a median follow-up of 30 months, one- and two-year PFS was 75% and 53%, respectively, and two-year OS was 95%. No grade three or higher toxicities were reported (69). Additionally, Milano *et al.* from the University of Rochester analyzed a subset of patients with breast cancer from two prospective trials investigating the use of HIGRT for oligometastatic disease. At initial publication, 40 patients were included, and four-year outcomes for patients treated with curative intent included OS of 59% and PFS of 38% (64). At longer term follow-up, 48 patients were included and they found some patients survived >10 years (60). In particular, patients with bone-only metastases had good outcomes, with 5- and 10-year overall survival of 83% and 75%, respectively, and 5-, and 10-year freedom from widespread metastases (FFWM) of 67% and 67%. Patients with non-bone metastases had lower 5- and 10-year OS of 31% and 17%, respectively, and 5- and 10-year FFWM of 30% and 15%, respectively. They also found fewer metastases (one *vs.* $>$ one) and number of involved organs (one *vs.* $>$ one) to be associated with improved FFWM in patients with non-bone metastases.

On the basis of these data, the NRG BR002 randomized phase II/III trial (NCT02364557) was designed, randomizing patients with oligometastatic breast cancer with controlled locoregional disease and four or fewer

Table 2 Retrospective and non-randomized prospective studies of metastasis-directed therapy (MDT) for metastatic breast cancer

Study	Institution	Metastatic sites	No. patients	No. metastases	Median follow-up	MDT techniques used	RT dose (Gy)	RT No. fractions	Disease progression	OS (median)	Grade 3+ toxicity (%)
Friedel <i>et al.</i> (49)	International Registry of Lung Metastases	Lung	467	1: 308 (66%); 2-3: 99 (21%); >3: 49 (10%); N/A: 11 (2%)	34 months	Surgery	N/A	N/A	N/A	Overall: 35 months; complete vs. incomplete resection: 37 vs. 25 months; DFI \geq 36 mo vs. <36 mo: 50 vs. 23 months	N/A
Abbott <i>et al.</i> (50)	MDACC	Liver	86	1: 53 (61%); >1: 33 (38%)	62 months	Surgery \pm RFA	N/A	N/A	Median PFS: 14 months	Overall: 57 months; ER+: 76.8 months; ER-/PR-: 28.3 months	N/A
Trovo <i>et al.</i> (69)	Multicenter, Italy	Extracranial	54	1: 27 (50%); 2-5: 27 (50%)	30 months	HIGRT and/ or IMRT	30-60 Gy	3-25	1-year PFS: 75%; 2-years: PFS: 53%	2-years: 95%	0
Scorsetti <i>et al.</i> (70)	Istituto Clinico Humanitas Cancer Center, Italy	Liver and lung	33	1: 21 (64%); 2: 1 (30%); 3: 2 (6%)	24 months	HIGRT	48-75 Gy	3-4	Median PFS: 11 months; 1-year PFS: 48%; 2-year PFS: 27%	Median: 48 months; 1-year: 93%; 2- and 3-year: 66%	0
Milano <i>et al.</i> (60)	University of Rochester	Extracranial; bone-only: 12 (25%); others: 36 (75%)	48	1: 19 (40%); 2: 15 (31%); 3: 7 (15%); 4: 3 (6%); 5: 4 (8%)	4.4 years for OS; 3.5 years for FFWM; 12.4 years for FFLR	HIGRT	Physician discretion; (typically 3-17 Gy/day)	Physician discretion (10 most common, n=27)	FFLR, Bone-only mets: 2-, 5-, & 10-years: 100%; Non-bone-only mets: 2-, 5-, & 10-years: 73%; FFWM, Bone-only mets; 2-years: 75%; 5-years: 67%; 10-years: 67%; non-bone-only mets; 2-years: 42%; 5-years: 30%; 10-years: 15%	Bone-only mets: 5-years: 31%; 10-years: 17%	N/A

RT, radiation therapy; PFS, progression-free survival; OS, overall survival; DFI, disease-free interval; RFA, radiofrequency ablation; HIGRT, hypofractionated image-guided radiation therapy; IMRT, intensity-modulated radiation therapy; FFLR, freedom from local recurrence; FFWM, freedom from widespread metastases; MDACC, MD Anderson Cancer Center

metastases to standard systemic and palliative therapy or ablative therapy (HIGRT or surgery) to all metastases (15). The primary endpoint of the phase II portion is improved PFS, and the primary endpoint of the phase III portion is improved OS. Additionally, circulating tumor cells (CTCs) are collected at baseline, after treatment, and at progression to determine whether CTCs are a predictive marker for improved outcomes. The phase II portion has completed accrual with 128 patients enrolled, and data are maturing. Depending on the results, NRG BR002 may continue to phase III with an accrual goal of an additional 232 patients.

Should patients with *de novo* oligometastatic disease undergo local therapy in addition to MDT?

For patients presenting with *de novo* oligometastatic disease (untreated primary tumor in addition to limited metastases), controversy exists regarding whether patients may benefit from surgery to the primary with or without adjuvant local radiotherapy versus systemic therapy alone. A recent NCDB analysis indicates that 43% of women diagnosed with stage IV breast cancer between 2003 and 2012 underwent surgical resection within the first year of their diagnosis despite lack of clear benefit (71). A multicenter prospective registry study (TBCRC 013) of patients with metastatic breast cancer analyzed 90 patients classified as responders to first line systemic therapy, 39 of whom subsequently underwent surgery to the primary disease site (72). No difference in 3-year OS was seen between responders who underwent surgery and those who did not (77% *vs.* 76%, $P=0.85$) regardless of ER and HER2 status. While older retrospective series suggested there may be a survival benefit to local therapy in this context (73-77), more recent randomized studies have shown mixed results.

An early study from India (Tata Memorial Hospital) enrolled 716 women with *de novo* metastatic breast cancer from 2005 to 2013 and randomized those who responded to upfront systemic therapy to receive locoregional treatment with surgery and adjuvant radiation. Median OS was no different in the locoregional treatment group compared to the no-locoregional treatment group (19.2 *vs.* 20.5 months, $P=0.79$) (78). However, this study has been criticized for suboptimal systemic therapy (e.g., limited taxane use; 92% of patients with HER2 positive disease did not receive anti-HER2 therapy).

A subsequent Turkish study (MF07-01) randomized 274 treatment-naïve patients between 2007 and 2012 with stage

IV breast cancer to receive locoregional treatment (LRT) followed by systemic therapy (ST) versus ST alone (79). At 3-year follow-up the survival rate was similar between the two groups (60% and 51%, respectively, $P=0.1$). However, with longer follow-up of 5 years, median survival was significantly improved for patients receiving local therapy, with a median survival of 46 months in the LRT group versus 37 months in the ST group (HR 0.66, 95% CI, 0.49–0.88, $P=0.005$). Unplanned subgroup analysis indicated survival advantage to local therapy for patients with ER+/PR+ disease, HER2/NEU negative disease, patients younger than 55 years of age, and patients with solitary bone-only metastases.

Additional randomized data is expected from the ongoing ECOG E2108 trial (NCT01242800) randomizing women with stage IV breast cancer who have not progressed during initial optimal systemic therapy to receive surgical resection followed by adjuvant radiation in the case of breast conservation and adjuvant radiation following mastectomy at physician discretion. This study is now closed to accrual after enrolling 390 participants. Preliminary data presented at ASCO 2020 demonstrated that at median follow-up of 59 months there was no significant difference between optimal systemic therapy plus locoregional therapy compared to optimal systemic therapy alone for 3-year OS (68.4% *vs.* 67.9%, HR 1.09, 90% CI, 0.80–1.49) or PFS ($P=0.40$). However, 3-year locoregional recurrence or progression was significantly higher in the systemic therapy alone arm (25.6% *vs.* 10.2%, $P=0.003$) (80). Final results are eagerly awaited to help inform locoregional decision making in the setting of *de novo* metastatic disease.

Do advances in systemic therapy change MDT?

In addition to more aggressive use of surgery and radiation directed at specific metastases, recent improvements in systemic therapies are altering the disease course of breast cancer and have potential implications on how and when to incorporate MDT. For example, the recent CLEOPATRA study changed standard of care for patients with metastatic HER2 positive breast cancer after demonstrating improved OS and PFS for patients receiving pertuzumab, trastuzumab, and docetaxel compared to placebo, trastuzumab, and docetaxel (81,82). In hormone receptor positive, HER2 negative metastatic breast cancer, cyclin-dependent kinase 4/6 inhibitors including palbociclib, ribociclib, and abemaciclib, are now being used in addition to hormonal therapy after multiple randomized phase III

trials demonstrated their use improves PFS and/or OS (16). Other targeted agents such as PI3K and PARP inhibitors are also being incorporated into the treatment of metastatic breast cancer to improve outcomes (17-20).

While systemic therapy is improving progression-free survival in patients with metastatic breast cancer, long-term complete remission with systemic therapy alone is rare (83-85). However, as these newer systemic therapies prolong the disease course, more providers may reasonably consider aggressive MDT with curative intent in patients with oligometastatic breast cancer. Progression in these patients often occurs at sites of known metastases rather than new metastatic locations (59,60), and therefore ablation of all known sites of cancer may maximize therapeutic benefit. Alternatively, some may say that we should hold off on MDT until all systemic options are depleted.

What about immunotherapy?

Immune checkpoint inhibitors have recently been incorporated into the treatment of certain metastatic triple-negative breast cancers after results of the Impassion 130 trial showed improved PFS and OS in patients with high PD-L1 tumor expression treated with nab-paclitaxel plus atezolizumab compared to patients receiving nab-paclitaxel alone (22). Additionally, in the non-metastatic setting, promising early results from the KEYNOTE-173 phase III trial of patients with stage II-III triple negative breast cancer treated with paclitaxel and carboplatin with or without pembrolizumab showed improved pathologic complete response in the pembrolizumab-chemotherapy group (64.8% vs. 51.2%, $P < 0.001$) (21). As immunotherapy becomes more commonplace in treatment algorithms for breast cancer patients, studies investigating its combination with HIGRT have demonstrated the combination to be safe and well tolerated. For example, a study of 79 patients treated with this combination had only 6 dose-limiting toxicities and no radiation dose reductions (86).

Beyond having an acceptable safety profile, radiation therapy may have an immune-mediated effect that works synergistically with immunotherapy. The so-called “abscopal effect,” in which radiotherapy to one site produces a response at a distant, non-irradiated site, was first described by Mole in 1953 and has since been reported multiple times in the literature, including in combination with immune checkpoint inhibitors (87-89). Ablative-doses of radiotherapy have been shown to have effects mediated by CD8+ T cells, as well as to increase type I interferon

responses (90,91). Based on these preclinical data, there has been growing interest in combining HIGRT with immunotherapy. For example, a phase I study investigated the use of HIGRT in either one, two, or three doses (20 Gy per fraction), followed by high-dose interleukin-2 (IL-2) for patients with metastatic melanoma or renal cell carcinoma. The combination was safe and demonstrated better-than-expected response rates in melanoma patients (71.4% PR or CR), hypothesized to be due to an immune-mediated response (92). However, to our knowledge the combination of HIGRT with immunotherapy has not been studied yet in breast cancer specifically, although in other diseases there are promising preliminary reports (93,94).

Are there non-curative benefits of HIGRT?

In addition to potentially improving OS and PFS, metastasis-directed HIGRT may have benefits such as symptom palliation and delaying systemic therapy. For patients who may typically receive palliative radiotherapy for painful bone metastases, HIGRT can similarly provide good pain control and potentially long-term local control (95). HIGRT for bone metastases has been shown to be well tolerated with limited grade three or greater toxicities (96). Additionally, a phase II/III randomized trial (RTOG 0631) investigated pain relief for painful bone metastases treated with HIGRT to the involved spine segments(s) versus conventional external beam radiotherapy to the involved spine plus one additional segment above and below (97). Initial phase III results demonstrated HIGRT was safe and well tolerated but showed no difference in pain relief at three months post-treatment between the two groups (98).

Another potential benefit to HIGRT for oligometastases and oligoprogressive lesions is delaying initiation of systemic therapy or transitioning to next-line therapy. The STOMP trial of patients with oligometastatic prostate cancer randomized to surveillance or MDT to all known sites of disease showed significantly longer ADT-free survival for the treatment group (13). Ranck *et al.* demonstrated that in patients with oligometastatic renal cell carcinoma, 64.2% of patients treated with metastasis-directed SBRT did not require systemic therapy at one year (99). HIGRT may be particularly useful in elderly patients who may not be candidates for or decline other treatment modalities, and HIGRT has been shown to have excellent rates of local control in these patients (86.8% at one year, 76.3% at two years) (70). Given these findings, HIGRT to oligometastases should be considered in certain

situations even in non-curative settings.

So which patients should be treated?

A number of factors must be considered when deciding which patients with oligometastatic breast cancer should be treated with metastasis-directed therapies, and this is an active area of investigation. Importantly, we await the results of the NRG BR002 phase III trial to help answer this question. In the meantime, one factor that should be considered is the number of metastatic sites and organs. Most trials, such as SABR-COMET have included patients with five or fewer metastases, although only 7% of patients on this trial had more than three metastases. Milano *et al.* found that both number of metastases and number of involved organs involved (1 *vs.* >1) were associated with improved OS and FFWM in patients with oligometastatic breast cancer with non-bone metastases treated with ablative MDT (60). Additionally, they showed improved OS and PFS in patients with bone-only metastases compared to non-bone metastases, suggesting these patients may warrant more aggressive therapy. Additionally, certain patients with hormone receptor positive disease may have a prolonged disease course in the setting of endocrine therapy, and ER+/PR+ disease has been shown to be associated with improved outcomes after metastasis-directed (50,60). Other potentially prognostic factors such as tumor microRNA expression and CTCs are under active investigation (15,62).

Conclusions

MDT is an effective treatment to control limited metastatic disease and potentially improve survival and progression-free survival in patients with oligometastatic breast cancer. High level, randomized data has emerged to support this approach for other primary disease sites, and research is ongoing for oligometastatic breast cancer specifically. MDT may be especially useful in breast cancer given its long natural history, particularly in the setting of improved systemic therapies including targeted agents and immunotherapy that prolong the disease course. Some patients with oligometastatic breast cancer treated with ablative therapy to all sites of disease have survival >10 years and may even be cured of their disease (60). Finally, the role of MDT in this patient population will be further clarified by the results of the ongoing NRG BR002 phase II/III randomized trial, and we eagerly await these results.

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