Review Article

Local therapies for managing oligometastatic breast cancer: a review

Hina Saeed[1]^, Anna M. Kirby[2]

[1]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [2]Department of Clinical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Sutton, London, UK

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Correspondence to: Hina Saeed. Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin USA.
Email: hisaeed@mcw.edu.

Abstract: The hypothesis that oligometastatic disease (OMD) may be cured through local eradication therapies has precipitated increasing research into the use of locally ablative therapies (LAT) for these patients. Advances in molecular biology have confirmed the presence of clinically and radiographically suspected oligometastatic state at the genomic level. At the same time, technological advances in different treatment modalities (primarily radiation and surgery) have allowed the administration of ablative doses to a broader spectrum of metastatic lesions. Despite increasing efficacy of modern systemic therapies, they are seldom curative. There is growing interest in identifying patients with truly oligometastatic breast cancer (OMBC) and in developing predictive biomarkers to determine which patients are more likely to benefit from LAT. In this review, we discuss data specific to the OMBC setting, the recent advances in understanding oligometastasis biology, the natural history of OMBC including diagnosis and classification, the theoretical basis for LAT, retrospective and prospective data supporting LAT, outcomes associated with LAT and ongoing prospective randomized trials designed to compare LAT and standard of care (SOC) therapies. We especially focus on LAT, primarily surgery and non-invasive stereotactic body radiation therapy (SBRT) for OMBC with references to other tumor types when these other tumor types inform OMBC treatment.

Keywords: Local; ablation; oligometastases; breast cancer

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Introduction

Contemporary insights into carcinogenesis have resulted in recognition of cancer as a multi-step process or a metastatic cascade rather than a binary phenomenon (1,2). This led to Hellman and Weichselbaum describing a new entity, "oligometastatic disease" (OMD) in 1995, as an intermediate state (limited in number of metastases and involved organs) in the spectrum of metastatic disease (3).

Recognition of oligometastatic breast cancer (OMBC) as "potentially curable" and a distinctive subset of metastatic breast cancer (MBC) together with knowledge of an invasion-metastases cascade has given rise to the idea that early eradication of metastases using local ablative therapies (LAT) could avoid subsequent dissemination (4). OMD can be classified by the timing of its appearance in relation to the primary disease and/or systemic therapies. Each OMD scenario will have a different standard-of-care approach and aim such that assessment of added benefits of LATs will

^ ORCID: 0000-0001-7751-3494.

require different endpoints (5).

Common sites of metastases for OMBC include bone, lung, liver, brain and lymph nodes (LN). LAT for OM disease have mainly involved surgery and/or stereotactic body radiation therapy (SBRT) with evolving modalities including radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). Against a background of increasingly complex systemic therapy (ST) approaches and improved survival, evaluating the added benefit of LATs in OMBC patients remains challenging.

This manuscript focuses on the current understanding of OMD, efforts to identify and classify OMBC, and published data on outcomes following LAT for OMBC whilst highlighting aspects where gaps in knowledge exist. A literature search was conducted in PubMed/MEDLINE for the terms "breast cancer" and "oligomet" to retrieve all relevant English-language articles. Citation chasing was conducted by analyzing the bibliography of references (backwards citation chasing) and through Google Scholar (forward citation chasing) (6).

Natural history of OMD

The definition of OMD comprises both the attempt to characterize those patients who are truly oligo- rather than polymetastatic such that LAT could influence the natural history of the disease, and the anatomical localization of oligometastases in order to be able to target them with LATs. Both aspects are discussed here.

Definition of OMD state

Based on clinical experience, Hellman and Weichselbaum described the concept of oligometastases as a clinically significant intermediate state of distant spread, reflecting disease with a low, slow and late metastatic spreading capacity (2,3). Since then, the concept has continued to mature and evolve.

There have been ongoing discussions around the number of metastases to be included under the term "oligometastasis". Published series have generally included up to 3–5 metastases in up to two organ systems (7-10). With variations in reporting, imaging sensitivity and absence of biological basis for lesion number or size, the maximum number of OMs in which use of LAT for all OMs would yield a clinical benefit over and above a change of ST is yet to be determined (11). As per the ASTRO-ESTRO consensus statement, an oligometastatic patient can be defined as an individual in which all the tumor locations are amenable to safe ablation with curative intent.

From a molecular standpoint, studies are increasingly confirming the basis for the OMD concept (12). Cancer progression is a multi-step process and, biologically, only a tiny proportion of cancer cells have clonogenic potential to successfully colonize secondary organs (1,13). With technology allowing increasingly granular resolution at the single cell genomic level, several hallmarks of cancer evolution have come into light: genotypic heterogeneity, immortality, presence of circulating tumor cells (CTCs) or circulating tumor DNA (ctDNA), dormancy, autophagy and phenotypic plasticity for resisting hostile selective pressures at distant sites. Somewhere during this transit, the cells presumably have not yet reached fuller metastatic potential and remain localized to a select few sites that provide a favorable niche (14-20). Additionally, unique mutations harbored by the primary tumor and metastatic lesions imply an ongoing branched pattern in genetic evolution once metastasis has occurred (21). At times, a solitary metastasis can be present for years as a single site of disease before subsequently seeding more widespread metastases and/or reseeding the primary tumor (22-25).

Some studies suggest that oligometastatic progression may be regulated at least in part by epigenetic alterations and potentially by microRNA (19-22 nucleotides regulating gene expression). MicroRNA profiling has allowed a more rigorous examination of the genomic underpinnings of a cell's metastatic potential. Analysis of a select panel of prospectively obtained microRNAs from the metastatic tumors of a cohort of patients with OMD subjected to radiotherapy revealed a distinct clustering of oligometastatic versus polymetastatic phenotypes with notable enrichment of microRNA200 in the polymetastatic samples (26). Other studies have also shown differential microRNA expression in slow versus rapid-progressing metastatic disease, with several of these implicated in metastatic cascade (27,28). In a cohort of MBC patients, microRNA expression profiling has been able to independently discriminate between oligo and polymetastatic breast cancer (29) thus supporting the concept of OMBC as a genetically distinct entity (28).

As yet however, in the clinic, there remain no validated molecular biomarkers that differentiate between the oligometastatic and polymetastatic states (11). In the meantime, rapid advances in imaging that allow identification of smaller metastatic deposits increase the likelihood of correctly identifying the oligometastatic state (30).

Anatomical localization of OMD

OMBC constitutes between 1% and 20% of all MBCs according to published literature although, with more recent advances in ST, the truth is likely to lie towards the top of that range (31,32). Identifying these patients is crucial both to offering local treatment with potentially curative intent and to optimizing resource utilization. Patients with a tendency towards polymetastatic disease will not benefit from LAT and should instead be considered for change of systemic approach.

Radiological identification of patients with OMBC is challenging. Most published series refer to an era before modern imaging, and thus many patients were probably under-staged, potentially leading to underestimation of the longer-term benefits of aggressive local management. Modern imaging with improved sensitivity and specificity has the potential to more accurately identify OMD, some of it in evolution to polymetastatic disease and some destined for indolent, non-progressive behavior. There remain, however, limitations in the sensitivity of modern imaging modalities. The risk of false positives also exists as validation by biopsy of multiple visualized lesions is usually impractical.

Anatomic sites for extracranial breast cancer metastases include bone, viscera (particularly lung and liver) and LN. For extracranial MBC, ^{18}F-FDG-PET/CT is an easily accessible imaging diagnostic tool with sensitivity of 90–94% and an accuracy rate of 83–90% (33,34). With bone being the first site of metastases for almost half of MBC patients and the most common site of metastases for estrogen receptor positive (ER+) disease, accurate identification of this subset of OMBC is critical. With bone-confined MBC, the natural history is usually characterized by an indolent course (35) with up to 20% alive at 5 years (36). Notably, solitary bone metastases have been significantly associated with prolonged OS (37). ^{18}F-FDG-PET/CT is more specific for metastatic bone disease than nuclear medicine bone scanning (38) and therefore is the preferred modality (39).

The incidence of lung metastases in MBC patients ranges between 23–36% with 6–10% of patients having lung-only metastases. A population-based study showed that increasing age, black race, high grade, human epidermal growth factor receptor 2 (HER2)-positive or triple-negative (TN) tumors were more likely to be associated with lung metastases (40). ^{18}F-FDG PET/CT remains the preferred approach for diagnosing pulmonary metastases in OMBC (41).

In liver, the sensitivity of ^{18}F-FDG-PET is limited for small metastases (<1 cm in diameter) due to liver motion during image acquisition and poor spatial resolution. MRI is superior for depicting and characterizing liver lesions compared to ultrasound, CT and ^{18}F-FDG PET/CT (42,43). The incidence of liver metastases in MBC patients is 40–50%. Growing evidence indicates that HER2-positive or TN tumors are more likely to be associated with liver metastases (44).

In relation to nodal disease, up to 5% of patients with early-stage breast cancer have regional nodal recurrence after breast conservation treatment (45-47). LAT appear effective in locally controlling LN oligometastases (48). Consequently, their identification through ultrasound, CT or ^{18}F-FDG-PET/CT is vital to improve OMBC outcomes.

Whole body-MRI (WB-MRI), like ^{18}F-FDG-PET/CT offers the advantage of multi-organ evaluation. Although some studies have emphasized the sensitivity of WB-MRI, one has also highlighted its poor specificity (82% of lesions on 1.5T WB-MRI DWI considered false-positive versus 11% on ^{18}F-FDG PET/CT) (49). Another study suggested equivalence of these techniques (WB-MRI versus ^{18}F-FDG PET/CT sensitivity 93% versus 91% and specificity 86% versus 90%) (50). Combined PET/MR imaging yields better sensitivity for liver and possibly bone metastases (41). ^{18}F-FDG PET/MR offers better classification of malignant versus benign lesions (51) compared with ^{18}F-FDG PET/CT, an important consideration in disease recurrence. Importantly, both WB-MRI and PET/MR, as compared to ^{18}F-FDG PET/CT, have accessibility and financial implications.

Although intracranial metastases occur in 0.4% of patients at presentation, this increases to ~8% (52) when other extracranial metastases are present, indicating that imaging (brain MRI) is warranted in the presence of extracranial disease (52) and/or suspicious neurologic symptoms. The risk of symptomatic intracranial metastases and a shorter brain metastases-free survival is more pronounced in TN and HER2-positive tumors compared with luminal or HER2-negative subtypes, potentially lowering the threshold for imaging (53-55). Other risk factors for the development of brain metastases include young age at diagnosis, presence of lung metastases, and short disease-free interval (DFI) (56-58). There is a suggestion that brain-only MBC, regardless of histology, has a better prognosis (59) supporting the use of a more aggressive local approach in these patients.

Imaging approaches should be tailored to the location and extent of OMBC at different points in the disease

trajectory such as initial diagnosis, response assessment and surveillance. From the perspective of response evaluation to systemic therapies, ^{18}F-FDG-PET/CT has the unique advantage of identifying persistent or progressive OMBC early on (39).

Oligocare (NCT03818503), a joint initiative between the European Society for Radiotherapy and Oncology (ESTRO) and the EORTC is a prospective, large-scale observational basket study for OMD patients. Optimal standardized quality imaging approaches are essential to interpret the data. Current evidence-based imaging guidance for Oligocare patients indicates that ^{18}F-FDG PET/CT is favored in breast cancer (with WB-MRI or PET/MR as alternatives) but needs supplementing with liver-specific MRI. At times, technologically 'advanced' imaging with better sensitivities and specificities may be preferred over standard imaging modalities. European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) provide imaging recommendations in the setting of high risk new primary or recurrent disease (39).

Classification of OMBC

Various scenarios of OMBC can present with similar imaging features and yet differ substantially from a clinical management perspective. Failure to consider the entire oncologic history could substantially affect clinical outcomes (60). Moving beyond the simplistic definition of oligometastasis, a recently published classification system based on five questions about the patient's clinical history and disease burden, provides guidance to highlight the existence of three broad categories of OMD: *de-novo*, repeat and induced. These categories can further be sub-divided into an array of nine clinical states, expanding upon clinical concepts that are already gaining momentum (5). These clinical states will each have distinct prognoses requiring different treatment approaches to accomplish unique goals and endpoints. Although the most frequently defined endpoints in OMD are local control (LC), overall survival (OS), progression-free survival (PFS), deferral of ST, maintenance of current ST and quality of life (QoL) (61), a recent consensus document has expanded on this spectrum providing guidance to match a specific scenario with a relevant endpoint (11).

Management of OMBC

Based on cohort studies, the resection or ablation of OMD has become standard therapy for several tumor sites such as colorectal cancer and renal cell carcinoma (62). In the case of OMBC, the goals for local management are distinct from those for MBC where local therapies are used for palliation or debulking. There is some evidence that women with low-volume OMBC may experience cure or improved PFS if all the tumor cells can be removed or treated effectively (32,63-67). In a prospective cohort of OMBC patients, OS of almost 50% was reported at 6 years (68). Recent developments in targeted systemic therapies might ultimately make the role of LC of residual and/or resistant lesions in OMBC more important. A unique advantage of local treatment is the subsequent reduction in the reservoir of potentially resistant clones especially in the context of ST induced selection pressure and prior to the clones' widespread dissemination (69-71).

Local management of the primary

The majority of current data pertaining to the local treatment of the primary site come from MBC in general. Several retrospective studies suggest an OS benefit from local management of the primary tumor in MBC (72-75). Potential reasons for this included selection bias (younger patients, better performance status, smaller tumor, more ER+ disease, lower metastatic burden), reversal of tumor-induced immunosuppression (76), decreased overall tumor burden and potentially resistant cell lines, removal of source as seeding new metastases (77), and increased chemosensitivity due to surgery-induced angiogenesis in distant disease sites. A notable limitation of these reviews includes lack of details around local and systemic therapies and therefore reduced applicability to current ST practice (73,78-81). By contrast, an analysis of two prospective non-interventional studies of MBC showed no difference in outcomes with the addition of local therapy to systemic management albeit that a subgroup analysis suggested a better prognosis following LAT for OMBC (82). Similar results were shown by a small prospective registry study (83). While the Indian prospective study showed no survival benefit with locoregional therapy, even for patients with limited disease (84), the Turkish study showed a benefit but was criticized for an unbalanced randomization (85). Most recently, the ECOG 2108 study presented at American Society of Clinical Oncology (ASCO) 2020 showed no survival or QoL benefit with local therapy in MBC (86).
These studies together suggest that local treatment of the primary is of questionable survival benefit in MBC. This is in

contrast to the prostate cancer setting where the randomized phase 3 STAMPEDE trial found that local radiation treatment of the primary prostate cancer alone, without locally ablative therapy to the metastases, improved OS in patients with a low metastatic burden, but not in those with a high metastatic burden, compared with androgen deprivation therapy only (87). Further well-designed randomized controlled trials (RCTs) in the OMBC setting may now be challenging given the large numbers required to demonstrate a survival advantage from radical management of primary disease in the OMBC setting. LC however remains an important endpoint such that many institutions would still recommend radical treatment of locoregional disease, particularly in the OMBC (as opposed to MBC) setting.

Locally ablative therapies (LAT)

Advances in treatment modalities have made it theoretically possible to ablate all detectable metastases in OMBC (88). Ablative treatment options for commonly treated sites in OMBC include surgery, SBRT, RFA and TACE. These modalities can be grouped together under the umbrella of LAT. It should be noted that the rapid adoption of LAT has occurred in the absence of randomized phase III evidence such that it remains challenging to select the population of patients in whom LATs have the greatest potential to prolong survival (89). As stated earlier the ESTRO-ASTRO consensus is that LATs be considered for patients for whom complete and safe ablation of all metastases is possible and in whom the pertinent oncologic scenario has been taken into account.

Management of extracranial metastases

Surgery

Bone is one of the most frequent sites of early metastatic disease in breast cancer and, as such, the presence of OMD disease in bone might represent the more indolent part of the metastatic process and therefore a point at which LAT may be able to influence the natural history of the disease. In a series of 115 MBC patients undergoing surgery (majority in the spine or proximal extremity), multivariate analysis showed that patients with solitary bone metastases had better survival compared to patients who had both bone and visceral disease (median OS of 65 versus 13 months) with no impact due to age or extent of surgery (90). Although sternal metastases are uncommon, they might be an extension of internal mammary LN eroding into the bone and as such have a better prognosis, particularly if solitary. In a small series of 9 patients with solitary sternal metastases and radical resection, a median survival of 30 months was reported (91). A retrospective review of 17 patients at Royal Marsden concluded that curative-intent *en-bloc* sternal resection for solitary sternal/parasternal breast cancer recurrence can provide good durable LC (77% at 5 years) and pain relief (92).

With respect to liver-directed LATs systematic reviews, retrospective cohorts and case series in MBC give conflicting results (66,93-95). This is also the case for OMBC. In a case-control study of 102 patients (only bone and ≤4 liver metastases allowed), half of whom underwent concurrent ST and liver resection and half of whom were matched non-surgery patients, there was a 3-fold higher risk of death on multivariate analysis without surgery (3-year survival of 50% versus 80% in non-surgery versus surgery cohort) (96). Predictive factors for better outcomes included ≤1 course of chemotherapy and absence of bone metastases. Other additional positive factors include a DFI of >2 years, solitary liver metastasis, absence of extrahepatic disease (except for isolated lung and bony metastasis), good systemic response, negative surgical margins and hormone responsiveness (97,98).

Similarly, there are no high-quality prospective trials to provide guidance for pulmonary resection in breast cancer (99). Historical cohort and case series have shown a large range in 5-year OS outcomes (36–62%) (64,100-105). A recent systematic review and meta-analysis of 15 retrospective and 1 prospective cohort studies encompassing almost 2,000 MBC patients with isolated pulmonary metastases undergoing local resection with or without concurrent ST showed a pooled 5-year OS of 46% (106). Predictive factors for improved OS included solitary pulmonary metastasis (pooled HR 1.30 for OS). Limitations include less than 5-year follow-up for majority of the studies, variable sample sizes, heterogeneous population and selective good performance status patients. Notably, several studies leaned towards favoring oligometastatic phenotype by excluding patients with extra-pulmonary metastases or even bilateral pulmonary metastases. Other additional positive factors include a DFI >3 years, solitary metastasis, hormone responsiveness, small metastases, and complete resection (32,63).

Radiotherapy

Given the number of organ systems that can be involved in OMBC and the invasive nature of surgery, there has been an effort to develop minimally or non-invasive methods for delivering LAT. SBRT or stereotactic ablative radiotherapy

(SABR) is an external radiotherapy technique that delivers highly conformal ablative doses [biologically effective dose (BED_{10}) >100 Gy] under precise image guidance. The technique is performed on an outpatient basis and involves only a few sessions (usually between 3 and 5), with little acute toxicity. Advances such as MR Linac and Cyberknife have the potential to further reduce toxicity with even tighter margins. SBRT is convenient and has no detrimental impact on QoL (107-109). Discussions around target volume, dose and treatment platform are beyond the scope of this review (110,111).

The majority of data supporting the use of SBRT come from retrospective and prospective non-randomized, mostly single arm studies (see *Table 1*).

(I) Studies of mixed cohorts

Milano *et al*. found that 39 breast cancer patients (within a 121 patient cohort of all histologies and ≤5 metastases) enrolled across two prospective studies of curative-intent SBRT (50 Gy/5 fractions), fared significantly better with respect to OS, PFS and LC than the whole mixed-histology cohort (126). No patient experienced Grade 4 or 5 toxicity, and only 1 patient experienced Grade 3 toxicity (nonmalignant pleural and pericardial effusion). Long term results were reported by the same group with median follow-up of 4.5 years for breast cancer patients (68). One-third of breast cancer patients were alive at the last follow-up visit (>4 to 10 years) without widespread metastatic disease. The 2- and 6-year OS rates were 74% and 47% respectively. The 2- and 6-year LC rate was 87%. Patients with progression of disease prior to SBRT initiation had a significantly worse 2-year OS rate compared to those who had at least stable disease (55% versus 81%). Fifty-seven percent long-term (>4 years) survivors had one initial metastatic lesion. Unlike other histologies, none of the OMBC patients who died 4 years after SBRT failed locally. None of the 17 bone lesions from breast cancer recurred after SBRT versus 10 of 68 lesions from other organs that recurred (P=0.095).

In a multi-institutional phase I/II trial of SBRT in 47 patients (63 lesions) with any primary tumor (4 with OMBC) and 1–3 liver metastases, patients received 36–60 Gy (118). The overall 2-year LC rate was 92% but, for lesions ≤3 cm 100%. Grade 3 and higher toxicity occurred in only 2% of patients. In another multi-institutional phase I/II trial of SBRT in 38 patients (63 lesions) with any primary tumor (2 with OMBC) and 1–3 lung metastases, patients received 48–60 Gy (119). LC at 1 and 2 years after SBRT was 100% and 96%, respectively. The incidence of grade 3 toxicity was 8%.

(II) Studies of breast cancer patients only

The longest-term data (30-year results) are reported in a retrospective review by Kobayashi *et al*. of 75 OMBC patients (120). With a preponderance of ER+, HER2-negative, low Ki67 (defined as <14%) patients and 60% with only one involved organ, the estimated median OS was 15 years. OS was significantly improved with single organ involvement, LAT (surgery or radiation), absence of liver metastases, and anthracycline-based chemotherapy. With LATs (n=35), the OS and relapse free rate at 10 years was 82% and 38% and at 20 years, 53% and 38% respectively.

Yoo *et al*. retrospectively reported on 50 OMBC patients (≤5 sites) (8). All patients had bone metastases and seven had pulmonary, hepatic, or LN metastases. Sixty percent had a single metastasis. With only one-third of patients receiving ≥50 Gy_{10} and inconsistent coverage of the entire lesion, the 2-year OS rate for all patients and solitary bone metastasis group were 85% and 97%, respectively. The 3-year LC rate was 70%. The presence of ER+ disease and solitary bone metastasis were independent favorable prognostic factors for survival.

Scorsetti *et al*. reported on an observational study of 33 OMBC patients with either lung (30%) or liver (70%) metastases treated with SBRT (121). Other metastatic sites stable or responding after chemotherapy were allowed and were not subjected to SBRT. Almost 70% were ER+. More than 90% of patients received systemic therapies for metastatic disease before and all of them after SBRT such that this was essentially a study of oligoprogressive or oligopersistent disease. The SBRT dose was higher than in previous studies at 56–75 Gy in 3 fractions and 48–60 Gy in 3-4 fractions, for liver and lung lesions respectively. Only two patients developed progressive disease within the treated target (both in liver). In this study, LC was excellent (1- and 2-year LC rates 98% and 90% respectively) compared to other studies of LATs for visceral lesions. This can be partially explained by the higher deposited dose to the target. There were no G3-4 toxicities. On univariate analysis, DFI >12 months, ER+ disease and medical therapies after SBRT showed a significant impact on OS.

Numerous retrospective and prospective studies have demonstrated the feasibility of SBRT for liver metastases with LC rates ranging between 70–100% at 1 year and 60–90% at 2 years (114,127-129). However, in these studies a wide range of doses and fractionations were used for SBRT delivery in very heterogeneous patient populations with different histologies and primary tumor sites. Onal *et al*.

Table 1 Summary of Radiation Therapy Trials including OMBC patients

Author/year	Disease	Design	Definition	Patients/n	Intervention	Local control (LC)	Progression free survival (PFS)	Overall survival (OS)	Notes
Milano 2012 (68)	Mixed	Prospective, Single Arm	≤5 lesions in 1-3 organs	121 (39 OMBC)	SBRT 50 Gy/10 fx	Breast: 2yr 87%; 6yr 87%	Breast Freedom from distant metastases 2yr 52%; 6yr 36%	Breast: 2yr 74%; 6yr 47%	
Salama 2012 (112)	Mixed	Prospective, Single Arm	≤5 lesions	61 (11.3% OMBC)	SBRT 24–60 Gy/4 fx		1yr 33.3%; 2yr 22%	1yr 81.5% 2yr 56.7%	Dose finding trial
Andratschke 2018 (113)	Mixed	Meta-analysis	≤4 Liver lesions	474 (13% OMBC)	SBRT	1yr 76%, (for breast 91%); 3yr 56%		1 yr 70%; 3 yr 29%	80% have 1 lesion
Goodman 2016 (114)	Mixed	Retrospective	≤3 liver lesions	81 (7.4% OMBC)	SBRT	4yr 91%		4yr 28%	
Bhattacharya 2015 (115)	Mixed	Retrospective	≤3 lesions	76 (18% OMBC)	SBRT 24–45 Gy/3–5 fx	89% (breast cohort had no local failures)	2yr 26.2%	2yr 63.2%	42% lymph node, 29% bone and spine
Fumagalli 2012 (116)	Mixed	Retrospective	≤5 liver or lung lesions	90 (9% OMBC)	SBRT 27–60 Gy/3 fx (median 45 Gy/3 fx)	1yr 84.5%; 2yr 66.1%	Median disease-free survival 6.7mo	OS 2yr 70%	
Mahadevan 2018 (117)	Mixed	Retrospective	Liver lesions (max # not defined)	427 (10% OMBC)	SBRT median dose 45 Gy [12–60]/3 fx	Median duration of LC 51mo		Median OS Breast 21mo	
Rusthoven (118)	Mixed	Prospective, multi-institutional Phase I/II	≤3 liver lesions (<6 cm)	47 (9% OMBC)	Phase I: SBRT 36–60 Gy/3 fx Phase II: SBRT 60 Gy/3 fx	Actuarial: 1yr 95%; 2yr 92%	Median PFS 6.1mo	Median OS 20.5mo	
Rusthoven (119)	Mixed	Prospective, multi-institutional Phase I/II	≤3 lung lesions (<7 cm)	38 (5% OMBC)	Phase I: SBRT 48–60 Gy/3 fx Phase II: SBRT 60 Gy/3 fx	1yr 100%; 2yr 96%	Median PFS 8.4mo	Median OS 19mo	
Kobayashi 2012 (120)	Breast	Retrospective	≤5 lesions per organ (except ≤10 in lung or bones) (1-2 organs, (≤5 cm lesion size)	75	Surgery or radiation in 35 patients	5yr 45%; 10yr 27.4%; 15yr 27.4%; 20yr 27.4%	5yr 56.8%; 10yr 32.8%; 15yr 29.1%; 20yr 29.1% Median PFS 68.5mo	5yr 79.2%; 10yr 59.2%; 15yr 51.2%; 20yr 34.1% Median OS 185mo	

Table 1 (*continued*)

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Author/year	Disease	Design	Definition	Patients/n	Intervention	Local control (LC)	Progression free survival (PFS)	Overall survival (OS)	Notes
Yoo 2015 (8)	Breast	Retrospective	≤5 sites	50 OMBC	RT 20–60 Gy (entire target not always covered)	3yr 70%; 5yr 66%	Distant PFS 3yr 37%	2yr 85% (96% for solitary bone lesion); 5yr 49%	60% had single lesion, 43/50 only had bone metastases, 2/3 <50 Gy_{10}
Scorsetti 2016 (121)	Breast	Observational	≤4 liver or lung lesions (<5 cm per lesion)	33	SBRT 48/4–60/3 for lung. 56.25–75 Gy/3 fx for liver	1yr 98%; 2yr 90%	1yr 48%; 2yr 27% Median PFS 11mo	1yr 93% 2yr 66% Median OS 48 mon	70% liver, 30% lung, 94% ≤2 lesions
Onal 2018 (122)	Breast	Retrospective	≤5 liver lesions	22	SBRT 54 Gy/3 fx	1yr 100%; 2yr 88%	1yr 38%; 2yr 8%	1yr 85%; 2yr 57%	
Milano 2009 (123)	Breast	Prospective	≤5 lesions	40	SBRT	4yr 89%	2yr 44%; 4yr 38% Median PFS 23mo Distant control: 2yr 50%; 4yr 43%	2yr 76%; 4yr 59%	35% liver, 30% lung, 28% bone, 23% thoracic lymph nodes, 70% ≤2 lesions
Trovo 2018 (124)	Breast	Prospective, Single Arm, Phase II	≤5 lesions	54	SBRT 30–45 Gy or IMRT 60 Gy	2yr 97%	2yr 53%	2yr 95%	70% bone, 25% lymph nodes
David 2020 (125)	Breast	Prospective, Single Arm	≤3 bone lesions	15	SBRT 20 Gy/1 fraction	Local PFS 2yr 100%	Distant PFS 2yr 67%		73% single lesion, 26% sternum

Table 2 Randomized phase II trials in oligometastatic disease

Trial name/author	Histology	Eligibility	Intervention	Benefit
SABR-COMET, Palma (109,130)	Multiple including breast	≤5 solid tumor metastases	SBRT	Median OS: 28 months versus 41 months (P=0.09) 5-year OS: 42.3% versus 17.7% (P=0.006). Median PFS 11.6 *vs.* 5.4 months and PFS at 5 years was 17.3% *vs.* 0% (P=0.001)
Gomez (131)	NSCLC	≤3 NSCLC metastases without progression after 3 months' systemic therapy	RT or surgery	Median OS: 17.0 months versus 41.2 months (P=0.017) Median PFS: 14.2 months versus 23.1 months (P=0.022)
Iyengar (132)	NSCLC	≤5 NSCLC metastases with stable disease after induction chemotherapy	SBRT	Median PFS: 3.5 months versus 9.7 months (P=0.01)
STOMP, Ost (133)	Prostate	≤3 asymptomatic, extracranial prostate metastases	RT or surgery	ADT-free survival: 13 months versus 21 months (P=0.11)
Oriole, Phillips (134)	Prostate	≤3 castrate-sensitive prostate metastases	SBRT	Median PFS: 5.8 months versus not reached (P=0.002)
EORTC 40004, Ruers (135)	Colorectal	≤10 unresectable colorectal liver metastases, no extrahepatic disease	RFA liver	Hazard ratio for OS: 0.58 (P=0.01)

ADT, androgen deprivation therapy.

recently reported on a retrospective review of 22 OMBC patients with 29 liver sites treated with SBRT to a dose of 54 Gy in 3 fractions (122). One- and two-year OS rates were 85% and 57%, PFS rates were 38% and 8%, and LC rates were 100% and 88%, respectively. No significant prognostic factors were found. There was no grade 4/5 toxicity.

Milano *et al*. reported on a prospective study of 40 breast cancer patients (85 lesions) treated with curative intent SBRT (123). The most common site of metastasis was liver [33] followed by lung [17], bones [17], thoracic LN [16] and pelvic or abdominal LN [2]. Eight patients had bone-only disease and 63% were ER+. Over 80% of patients had only one organ and a maximum of 3 lesions involved. ST was administered prior and after SBRT in 36 and 32 cases, respectively. Two- and four-year OS were 76% and 59%, respectively. The 4-year ultimate PFS (incorporating salvage therapy for local failure) was 43%, and tumor LC 89%. No lesions failed locally after 18 months. Patients with bone metastases (n=11) experienced an improved PFS (P=0.037). All 8 patients with bone-only metastases remained alive, and 7 of 8 are with no evidence of disease recurrence at 22–89 months (median 50).

Trovo *et al*. reported on a multicenter phase II study for 54 OMBC patients {92 lesions including bone [60], LN [23], liver [5] and lungs [4]}. They showed that treatment with SBRT (30–45 Gy/3 fractions) or intensity-modulated radiation therapy (60 Gy/25 fractions) resulted in favorable outcomes (2-year PFS 53%, LC 97%, OS 95%) without any acute grade ≥3 toxicity (124).

A recent prospective single institution study by David *et al*. reported on 15 patients (73% luminal) with ≤3 bone only oligometastases treated with SBRT (20 Gy/1 fraction) (125). The treatment was safe and feasible with 2-year LC of 100% and 2-year PFS 65%. Of 19 treated metastatic sites, five were sternal metastases that were all safely treated. SBRT provides a significantly less invasive alternative to surgical approach in selected patients.

Together, the above findings indicate that the most favorable group for use of LATs in OMBC would be patients with solitary bone metastasis and ER+ disease. Despite good LC for visceral metastases, survival outcomes remain inferior when compared to bone-only disease. Other favorable factors include long DFI and receipt of ST.

(III) Randomized studies

After decades of hypothesis-generating retrospective reports, the value of integrating SBRT into the treatment pathway for OMD was investigated in six randomized phase 2 studies with improvement in either PFS and/or OS (see *Table 2*) (130-135).

One of the larger studies (SABR-COMET) (130) of 99 patients (≤5 lesions in ≤3 per organs) included 18 OMBC patients with controlled primary malignancy. This study showed, for the whole trial population, an OS benefit with SBRT in addition to standard of care (SOC) [41 months in SBRT arm versus 28 months for SOC alone (HR 0.57,

95% CI, 0.3–1.1, P=0.090), noting a prespecified two-sided alpha of 0.20 as part of a phase II screening trial], doubling of PFS to 12 months from 6 months (HR 0.47, 95% CI, 0.3–0.76, P=0.0012) and LC of 75% versus 49% in SBRT versus control arm respectively. However, there was an absolute increase of 20% in the rate of adverse events of ≥ grade 2 in the SBRT arm, with treatment-related deaths occurring in three (from pulmonary abscess, subdural hemorrhage and pneumonitis) of 66 patients after SBRT, compared with none in the control group. At a glance the first two treatment related deaths would not be typically expected secondary to SBRT, whilst the last case appears to be attributable to SBRT (136). About half of the lesions were in the lung, one-third in bone and 75% of patients had ≤2 sites. With extended follow-up, the impact of SBRT on OS was larger in magnitude than in the initial analysis and durable over time (SBRT versus control arm: median survival 50 versus 28 months, OS at 5 years was 42.3% versus 17.7%, median PFS 11.6 versus 5.4 months and PFS at 5 years was 17.3% versus 0%). A comparatively lower magnitude of PFS benefit from SBRT in the setting of longer OS benefit and significant rates of salvage SABR (9 versus 1 patient) might indicate the presence of undetected micrometastatic disease at presentation. With close surveillance and salvage SBRT at progression, it is apparent that post-progression treatment is influencing OS benefit. There were no new safety signals, and SBRT had no detrimental impact on QoL (109).

Other LAT modalities

In unresectable or high-risk surgical liver metastases patients, alternatives to surgery and radiation include RFA and TACE (137-139). Both appear to have low adverse event rates. There are no trials comparing the two modalities, though there is some evidence that the combination appears to be safe and superior to RFA alone (140).

RFA offers effective LC especially for solitary lesions <3 cm in diameter and in those for which a 10-mm margin of ablation could be achieved (141,142). A study comparing laparoscopic liver RFA in MBC patients (who either had no or incomplete response to ST) with patients treated with ST alone reported 47 months OS in the RFA group and 9 months in the ST only group (P=0.0001) (143). A meta-analysis of 14 studies evaluated the efficacy of RFA compared to hepatic resection in MBC patients and found the hepatic resection to be more efficacious (5-year OS combined OR 0.38, P<0.001) although RFA gives rise to fewer postoperative complications and shorter hospital stays (144). The mortality and morbidity with RFA ranges from 0.3% to 0.8% and 2% to 10% respectively (141).

Data suggest that TACE may result in tumor shrinkage and facilitate curative intent resection in patients (145). A retrospective review of MBC patients with liver-only metastases compared combined TACE and ST to ST alone and found 3-year OS of 47.6% in the combined treatment group versus 7.4% in the ST alone group (P=0.027) (146).

Additional low-toxicity local procedures include cryosurgery, laser-induced interstitial thermotherapy, microwave ablation, high-intensity focused ultrasound (HIFU), or tumor embolization with isotope-loaded microspheres (147,148).

Management of intracranial metastases

The optimal treatment of brain metastases remains controversial. Surgery or stereotactic radiosurgery (SRS), possibly integrated with whole brain radiation therapy (WBRT) are available options. The intrinsic breast cancer subtype (basal, luminal A/B, HER2-positive) is a key determinant of prognosis (149,150). Historically, breast cancer is not well represented in published phase III randomized studies of SRS (7–12% of the study populations) (151). Indeed, there are few data specifically addressing different breast cancer subtypes despite the fact that management of extracranial disease differs widely based on subtypes. Future studies specifically addressing treatment outcomes for well-defined patient groups and different tumor subtypes are needed. The number of brain metastases is also an important prognostic factor for survival as well as influencing treatment selection (152).

Broadly speaking, SRS is now the primary treatment for patients with either limited or multiple brain metastases, with potential synergistic effects when combined with certain immunotherapies or targeted therapies (153-155). Fractionated SRS (2–5 fractions) can be considered for patients with large metastases (>2 cm in diameter), recurrent lesions after prior SRS, postoperative cavities or metastases located near sensitive structures (156,157).

Surgery improves the survival outcomes of patients with a single brain-metastatic lesion, a good KPS and a limited number of extracranial metastases (158,159). Postoperative SRS is an alternative to WBRT for patients who undergo resection of brain metastases, with a reduced risk of neurocognitive decline. However, SRS is associated with an increased risk of intracranial failure compared to WBRT, albeit without a corresponding decrement in OS (160). With new systemic therapies showing promising CNS activity they could act as a "whole brain irradiation"

surrogate to control brain micrometastatic disease leaving SRS to control macroscopic foci (161-164). Recent data favors preoperative SRS versus postoperative SRS due to lower risks of radiation necrosis and leptomeningeal disease (165-167).

Ongoing studies and future directions

Studies of OMD are limited by statistical bias and tumor and patient heterogeneity. There are few high-quality published data regarding identification and treatment of OMBC. However increased awareness of OMBC has resulted in several active prospective phase II/III RCTs (see *Table 3*).

Multiple trials are evaluating the use of SBRT and/or traditional surgery in addition to SOC ST in the first line setting for newly diagnosed OMBC [e.g., CLEAR NCT03750396 (168); STEREO-SEIN NCT02089100 (169); NRG BR-002 NCT02364557 (170); NCT02581670 (171), PROMISE-005 NCT03808337 (179)]. A novel pilot phase I study in Australia, evaluating the role of SBRT followed by 6 months of anti-PD1 therapy with pembrolizumab, with a goal of showing both safety and enhanced immune activation, has been recently completed [BOSTON-II, NCT02303366 (172)]. This strategy is of particular interest, given its recent success in lung cancer where a phase II single arm study showed a 13-month PFS benefit compared to historical controls in oligometastatic non-small cell lung cancer (NSCLC) (180). AZTEC (NCT03464942) (173) is evaluating the role of SBRT followed by atezolizumab in TN breast cancer. SABR-COMET-3 (NCT03862911) (175) and SABR-COMET-10 (NCT03721341) (176) are assessing the impact of SBRT on OS in patients with 1-3 and 4-10 metastases, respectively, and accruing patients with a controlled primary tumor of any solid tumor histology including breast. The modification of the number of metastases compared with SABR-COMET is due to the fact that >90% of patients enrolled on it had ≤3 lesions. The expansion of up to 10 metastases in SABR-COMET-10 will allow exploration of the clinical benefits of LAT in patients with more widespread disease. The CORE trial (NCT02759783) (177) is a phase II trial of SBRT with a controlled primary tumor (breast, NSCLC or prostate) and 1-3 metastatic lesions. Not only are these trials prospective and many of them randomized, they also comprise patient populations exposed to modern, guideline-based systemic therapies e.g., endocrine-CDK4/6 inhibitor or mTOR inhibitors.

Currently, a concern with the aforementioned research studies is that they effectively preselect patients for enrollment based upon having an existing oligometastatic presentation. A proactive imaging protocol such as BCMetPats study (NCT027069640) (181) can evaluate the usefulness of early detection of oligometastases by whole body PET-CT, CT and brain MRI in breast cancer patients with high-risk (>30%) for developing metastatic disease. By documenting the patterns of early metastatic spread of breast cancer, it can potentially provide insight to determine optimal future surveillance imaging protocols with respect to the time to progression, rate of tumor growth and affected organs.

To facilitate comparison of trial results and uniformity in future trial designs, it would be prudent to adopt the consensus definition and the appropriate scenario of OMBC as well as the corresponding endpoint. Two ongoing challenges exist (I) determining which patients truly have OMD and (II) ascertaining who is most likely to experience a meaningful response to LAT. To answer the former, advanced and consistent imaging and circulating biomarkers, such as microRNA and ctDNA may improve our ability to characterize disease burden and behavior. To address the latter requires a more complete understanding of response to radiotherapy, metastatic process and the immune system. A deeper understanding of this process and subsequent development of predictive biomarkers may be obtained through sequencing of biopsy or liquid biopsy specimens to explore relationships and lineages of specific metastases in these patients or through advances in analysis of circulating readouts, such as CTCs, ctDNA, and circulating T cell repertoires. With many of the ongoing trials planning to obtain such exploratory biological correlates, careful analysis of these will be valuable in increasing our understanding of metastatic biology as well as which patients obtain clinical benefit from LAT.

Conclusions

Given ongoing improvements in ST, up to a fifth of MBC patients are now presenting with OMBC. Imaging techniques for identifying OMBC are improving and classification of OMBC scenarios as per ASTRO-ESTRO consensus will help in evaluating outcomes of LAT at different points in the disease's evolution. RCT data from a mixed patient cohort hints at likely OS benefits of SBRT in the OMBC setting. Ongoing prospective and randomized studies will help to define subgroups most likely to gain from ablative treatment of OMBC but are challenging to

Table 3 Summary of Ongoing/Recently completed Clinical Trials of SBRT in OMBC Patients

Principal Investigator	NCT	Disease	Design	Definition	Target Accrual	Intervention	Outcome
Jeong (168)	NCT03750396	ER-positive/ HER2-negative; Breast cancer	Single arm, Phase II, multicenter	≤2 lesions (Size ≤3 cm) in single organ or site	110	CLEAR: Local treatment (SBRT/surgery/RFA) in addition to endocrine therapy (CDK4/6 inhibitor or mTOR inhibitors)	Primary: PFS; Secondary: OS
Bourgier (169)	NCT02089100	De novo oliogmetastatic breast cancer	Randomized, Phase III, multicenter	≤5 lesions (each ≤10 cm or ≤500 mL, ≤7 cm for liver)	280	STEREO-SEIN: SBRT + systemic treatment *vs.* systemic treatment alone	Primary: PFS; Secondary: LF, OS
Chmura (170)	NCT02364557, NRG BR-002 Phase II accrual met in 2019	Breast	Randomized Phase II/III	≤4 lesions (≤5 cm each)	402	Standard of care *vs.* Standard of care + SBRT and/or surgery	Primary: PFS, OS; Secondary: Presence of CTC (baseline, after treatment); levels of ctDNA; incidence AE's; appearance of new metastases
De Rose, Comito (171)	NCT02581670	Breast *Lung/Liver Metastases	Non-Randomized Phase II	≤4 lesions (< 5 cm)	58	SBRT to medically inoperable lung and liver lesions	Primary: Local Control, Toxicity Secondary: PFS, OS
Steven, Loi (172)	NCT02303366 (Completed)	Breast	Prospective single arm Phase I	≤5 lesions	15	BOSTON-II, SBRT (20 Gy x1) + MK-3475 (Pembrolizumab) x 8 cycles	Primary: Acute and late adverse events; Secondary: Immunological effects, efficacy
Steven, Loi (173)	NCT03464942	Breast (triple negative)	Randomized Phase II multicenter	≤4 lesions with at least one untreated lesion	52	AZTEC, (20 Gy ×1 *vs.* 8 Gy ×3). SBRT followed by Atezolizumab ×24 months	Primary: PFS; Secondary: Response, safety, OS
Dirix (174)	NCT03486431 (Completed)	Mixed	Prospective, Phase I	≤3 lesions (<5 cm)	90	Destroy: Dose-escalation Trial for Non-spine Bone & Lymph Node Oligometastates; SBRT (5×7 Gy, 3×10 Gy, 1×20 Gy)	Primary: DLT; Secondary: Median PFS; Local Control Rate
Olson (175)	NCT03862911	Mixed	Randomized Phase III	≤3 lesions (intracranial included)	297	SABR-COMET 3: standard of care with and without SBRT	Primary: OS; Secondary: Toxicity, PFS, QoL, CTC, ctDNA
Palma (176)	NCT03721341	Mixed	Randomized Phase III	4–10 lesions (intracranial included)	159	SABR-COMET 10: standard of care with and without SBRT	Primary: OS; Secondary: Toxicity, PFS, QoL
Khoo (177)	NCT02759783	Breast, Prostate, NSCLC	Randomized Phase II multicenter	≤3 lesions in ≤2 organs	245	CORE: Standard of Care +/– SBRT to extracranial metastases	Primary: PFS; Secondary: OS, Local Control, Toxicity
Tsai (178)	NCT03808662	Triple negative breast cancer, non-small cell lung cancer	Randomized Phase II	≤5 progressing lesions	160	PROMISE-004: Precision Radiation for OligoMetastatIc and MetaStatic DiseasE (PROMISE)-004: Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression	Primary: PFS; Secondary: OS
Yang (179)	NCT03808337	Triple negative breast cancer, non-small cell lung cancer	Randomized Phase II	≤5 lesions	142	PROMISE-005: Standard of Care +/– SBRT in breast and lung cancer	Primary: PFS; Secondary: OS

fund and accrue and take time to deliver outcome data.

In the meantime, SBRT has been widely adopted in radiation oncology. Recognizing the need to address gaps in current knowledge before increasing clinical experience and expert opinion alter the balance of equipoise, Oligocare, a prospective registry, for collecting data on baseline factors and outcomes in patients undergoing SBRT for OMD has been established. Collection of detailed prospective data in large patient numbers provides another means of identifying factors predictive of those in whom SBRT will be associated with the most durable benefits. Ongoing efforts to understand the biological mechanisms underpinning metastatic potential will also help us refine our definitions of OMBC, determine how LATs interact with the biology of OMBC, and improve patient selection for ablative therapies including SBRT.

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