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Oligometastatic Breast Cancer

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Introduction

Breast cancer remains the most common cancer in women worldwide, and the second leading cause of cancer-specific death[1]. Most breast cancer-specific mortality can be attributed to sequelae of distant recurrence / metastasis. About 6% of metastatic breast cancer (MBC) cases arise de novo, and an estimated 20–30% of all early stage breast cancers recur at distant sites[2]. MBC represents a spectrum of disease, both biologically as well as clinically in terms of proclivity for certain sites (e.g. bone predominant in hormone receptor positive disease) and disease burden. A subset of patients with MBC will present with limited disease, often defined as ≤5 deposits, termed 'oligometastatic' breast cancer (OMBC). Although the incidence of OMBC is not well characterized, there is some data to suggest a significant proportion of all new MBC presents as oligometastatic disease. For instance, one tri-institutional retrospective analysis of 2,249 patients with stage I-III disease who had first treatment failure found that 21.9% were characterized as having oligometastasis[3]. This delineation between oligo- and poly-metastatic disease is recognized increasingly as far more than an arbitrary differentiation; there are treatment and survival implications. For example, the oligometastatic patients in the review cited above were followed for ≥3 years and were found to have significantly longer overall survival (OS) as compared to polymetastatic patients.

Although the term 'oligometastatic' has been part of common clinical parlance since its introduction in 1995 by Hellman and colleagues[4], our conceptualization of this entity continues to evolve. Prior reviews on this subject have focused on outcomes with local techniques e.g. stereotactic radiation and surgery. In the last decade, novel analytic techniques have led to significant insights into disease biology with the aim of informing next generation treatment strategies. As such, we aim to bring the reader up to speed on the current *molecular* understanding of this unique disease entity. Having a deeper biologic understanding of oligometastatic cancer will help conceptualize a framework for treatment options. We also provide a historical perspective on OMBC, a review of the current treatment paradigms, and a discussion on clinical trials evaluating new approaches for treating OMBC.

A Historical Perspective

For over a century, clinicians, surgeons, and scientists have all sought to define the mechanism of progression of breast cancer from a localized, curable surgical disease to systemic, incurable disease. William Halstead, a prominent Johns Hopkins surgeon, described breast cancer as a local disease that spread in a contiguous fashion to lymph nodes

and then systemically[5, 6]. From this concept, the anatomic staging system was developed in 1959 to aid in selecting patients for surgery[7], which at that time was the Halstedian approach of radical mastectomy[6]. Subsequent to this, a ‘systemic’ model of disease was proposed, whereby cancer was thought of as either localized or systemic at diagnosis, and hence if patients had positive lymph nodes, the systemic model would assume they had a high probability of metastasis[8]. This model, in turn, gave rise to the now universally accepted concept of adjuvant systemic therapy. In 1995, Hellman and colleagues defined a new entity, *oligometastasis*, reflecting contemporary insights into carcinogenesis; namely, that cancer progression is a multi-step process, rather than a binary phenomenon of whether or not metastasis is present and widespread[4]. They proposed that at this stage, the cancer’s full metastatic potential was not yet reached, limiting it to certain sites in the body that were *receptive* to the cancer, implicating the ‘seed and soil’ theory originally proposed in 1889 by Stephen Paget[8]. Since then they and others have propelled the field of OMBC forward by attempting to understand this state at the genomic level.

Biologic Basis for Oligometastatic Disease: What we know.

Our biologic understanding of carcinogenesis and evolution from primary tumor through an intermediate ‘disseminated tumor cell’ state to overt metastatic disease continues to evolve as we utilize highly sophisticated analytic techniques to achieve increasingly granular resolution at the single cell genomic level. As we have come to understand, there are several hallmarks of a cancer’s metastatic potential. Genotypic diversity, immortality, and phenotypic plasticity at distant sites are some of the more relevant features[9]. Studies have shown that primary tumors release a subpopulation of genetically immature cells (hereby referred to as disseminated tumor cells, or DTC’s), which travel through the blood (also known as circulating tumor cells, or CTC’s), and deposit in the bone marrow where they enter a state of dormancy and rely on autophagy among other mechanisms for self-maintenance[10–12]. At some later point, they exit dormancy and acquire further genetic changes that enable a more phenotypically plastic cell, thereby allowing it to resist hostile selective pressures at distant sites. Somewhere in this transit period, the cells presumably have not yet reached their full metastatic potential and can achieve metastasis in a select few sites that provide a more favorable niche[13].

Far from a linear pathway, however, genetic evolution in the metastatic process seems to proceed in a branched pattern. In one study, matched samples of patients with primary HER2+ breast cancer, brain metastases, and normal tissue were sequenced and evaluated for both shared and unique mutations in several key oncogenes and tumor suppressors. Although most patients had a set of shared mutations, both the primary tumor and the brain metastases harbored unique mutations implicating that both primary and metastatic lesions continued to evolve separately once metastasis had occurred[14].

More recently, micro RNA (miRNA) profiling has allowed a more rigorous examination of the genomic underpinnings of a cell’s metastatic potential. In an elegant study intending to genotypically identify oligo- and poly-metastatic disease, Lussier et al. performed miRNA expression profiling of a cohort of patients with oligo-metastatic disease who underwent radiation therapy and prospectively followed them for progression. While some of these

patients went on to develop extensive poly-metastatic disease, others had a very stable disease course. Unsupervised clustering analysis of a select panel of miRNAs from the metastatic tumors (but not the primary tumors) revealed a clear clustering of an OM phenotype and a poly-metastatic phenotype. Notably, miR-200c was identified as particularly enriched in the metastatic samples, and subsequent mouse xenograft models with oligo- and poly-metastatic cell lines with injection of miR-200c versus control showed that this miRNA was able to convert oligo-metastatic phenotype to poly-metastatic phenotype, implicating mi-R200c as a potential mediator for transition from OM to poly-metastatic disease[15]. Other studies have also shown differential miRNA expression in slow versus rapid-progressing metastatic disease, with several of the miRNA's identified in the slow-progressing phenotype shown to regulate cellular adhesion, migration, and invasion[16, 17]. These findings have already led to pre-clinical work in mouse models demonstrating potential targetability of the miRNA pathways to suppress metastatic potential[18]. Moreover, miRNA expression analysis was able to independently discriminate between OM and poly-metastatic breast cancer in a separate cohort of patients with impressive accuracy[19]. Taken together, these data support the notion of OM as a *genetically distinct* entity rather than just a 'transition point' from primary tumor to widespread metastasis.

Further work building on these studies will hopefully yield an array of clinically relevant products, including validated tools for discriminating between true OMBC from poly-metastatic breast cancer, an integrated staging system incorporating both genomic and clinical features[20], and appropriate targets (e.g. the miRNA's described above) for new systemic therapies.

Radiation Therapy in OMBC

Due to the limited extent of disease burden, OMBC lends itself nicely to non-invasive modalities with high precision, such as radiotherapy, and indeed this has been utilized with increasing frequency[21]. Until recently, most data supporting its use came from retrospective and prospective non-randomized, mostly single arm studies (see Table 1 for list of selected studies)[22, 23, 32–36, 24–31]. For example, one study prospectively followed 121 patients with various oligometastatic cancers, including a cohort of 39 breast cancers, who underwent stereotactic body radiotherapy (SBRT). OM was defined as ≤5 lesions in ≤3 organs. For the breast cancer cohort, two year overall survival, freedom from widespread metastasis, and local control rates were 74%, 52%, and 87%, respectively[37]. Bone metastases in particular were amenable to radiotherapy, with no lesions recurring as opposed to 10 of 68 lesions in other organs recurring. Another phase II prospective single arm trial of 52 breast cancer patients with oligometastasis (defined as ≤5 metastatic sites) receiving SBRT or intensity modulated radiotherapy (IMRT) achieved a 53% 2 year progression free survival and 2 year local control rate of 97%, without incurring any grade ≥3 toxicity, supporting the use of radiotherapy as a treatment modality for oligometastatic disease[35].

Because of the significant heterogeneity in the small case series / cohort studies in publication, it has been difficult to draw firm conclusions. One systematic review evaluated 41 observational cohort studies and was not able to find any clear signal for improvement in

outcomes with locally ablative therapies (though it should be noted that about half were radiation and the other half surgery), further arguing for prospective randomized trials[38].

Until recently, these non-randomized studies were all that clinicians had to aid in clinical decision making. However, results from a large prospective *randomized* phase II trial have now been published with encouraging results. Palma and colleagues evaluated the efficacy of stereotactic ablative radiotherapy (SABR) in 99 patients with various cancers, each with up to 5 distant lesions. The majority of cancers were breast, lung and prostate. The control group received standard of care palliative therapy (systemic therapy and non-SABR radiotherapy as deemed clinically appropriate). With a median follow up of 25 months, the primary endpoint of overall survival was significantly increased from 28 months in the control arm to 41 months in the SABR arm (HR 0.57, 95% CI 0.3–1.1, p=0.090, noting a prespecified two-sided alpha of 0.20). Furthermore, progression free survival was doubled from 6 months to 12 months (HR 0.47, 95% CI 0.3–0.76, p=0.0012). Notably, this treatment did lead to grade 5 toxicity in 3 patients (from pneumonitis, pulmonary abscess, and subdural hemorrhage). Although this trial encompassed several cancers, it should be noted that breast cancer was among the most common subtypes[39]. Reviewing the experience in oligometastatic lung cancer (OMLC), a prospective randomized phase II trial of 49 patients with OMLC (≤4 lesions), whose lesions were considered stable after first line therapy, compared standard of care treatment to local consolidative therapy (LCT) with radiation. The primary endpoint of progression free survival was improved with LCT (4.4 months in control arm vs 14.2 months in LCT arm, p=0.022). Overall survival, a secondary endpoint, was also improved with LCT (41.2 months vs 17 months, p=0.017)[40]. Yet another phase II randomized trial in limited metastatic non-small cell lung cancer evaluating SABR plus chemotherapy vs chemotherapy alone further demonstrated a significant progression free survival benefit with the addition of SABR[41]. Taken together, these *prospective* trials utilizing local control of oligometastatic cancer are demonstrating survival benefits. Although conclusive data regarding the role for local radio-ablative treatment does not yet exist specifically for breast cancer, there is an ongoing phase II/III randomized trial by the NRG to answer this question for OMBC[42]. We eagerly await these results, with an estimated primary study closure date of 2022.

Surgery in OM.

The role of surgery in MBC has been explored in two fundamentally different approaches: resection of the primary tumor and resection of metastatic deposits (metastasectomy). The majority of data in support of these strategies is retrospective in nature and hence must be interpreted with caution. We review both strategies below.

Primary tumor resection

Studies evaluating the role of resection of the primary tumor in the context of MBC and specifically OMBC have produced mixed results. Proposed mechanisms for benefit stem from preclinical mouse model experiments. One such study using an orthotopic breast cancer mouse model showed that reduction in tumor burden via primary tumor resection not only halted further metastatic progression, but resulted in reduced splenic myeloid-derived

suppressor cells and increased CD4 and CD8 positive T cells, suggesting an enhanced immune response[43]. To date, however, these data have not been *conclusively* replicated in humans. For instance, a propensity matched retrospective analysis using Surveillance, Epidemiology, and End Results (SEER) data of 29,916 MBC patients, half of whom underwent primary tumor resection, showed an association with increased overall survival of 16 months compared to no surgery, particularly in patients with limited sites of disease[44]. However, this study looked back as far as the 1980's, before modern day systemic therapies were in use, thus capturing a population not necessarily reflective of today's treatment paradigms. By contrast, an analysis of two prospective trials of *de novo* MBC patients who underwent surgery of the primary tumor (N=568) showed no difference in PFS and OS compared to their non-surgical counterparts[45]. The first cohort reflected an observational trial of HER2 positive MBC receiving trastuzumab +/− palliative single agent chemotherapy, while the second cohort represented HER2 negative patients receiving bevacizumab plus taxane as first line therapy in the metastatic setting. High metastatic tumor burden, defined as ≥3 sites of disease, was a poor prognostic marker, suggesting that patients with oligometastatic disease fared better. Another retrospective study of 530 patients with *de novo* MBC patients who underwent surgery of the primary site within 12 months of diagnosis found improved PFS and OS as compared to those who did not, with ≤3 lesions at diagnosis a positive prognostic marker for survival[46]. The retrospective nature of all these analyses does limit our confidence in these associations. One of the few prospective trials on this topic is an RCT comparing locoregional surgery (mainly modified radical mastectomy) vs not in 350 patients with *de novo* MBC. Approximately 25% of patients had oligometastatic disease with ≤3 metastases, and about 60–70% were ER positive, HER2 negative. Almost all surgical patients had been pre-treated with chemotherapy. There was no PFS or OS improvement found by undergoing surgery, and on subgroup analysis the OMBC patients also did not benefit[47]. Keeping in mind this was a single institution experience, these findings support the negative results of several pooled analyses on this topic and hence there is insufficient evidence to recommend this in routine practice at this time.

Liver Metastasectomy

Resection of isolated focal metastases to the liver has been shown to improve outcomes in other tumor types, such as colon cancer [48, 49]. In metastatic breast cancer, fifteen percent of patients are estimated to present with liver involvement[50], prompting consideration of local therapy as an adjunct to systemic therapy. Unfortunately, there have been no prospective randomized trials to inform the benefit of such an approach. However, several cohorts and case series have been published, and a number of systematic reviews have summarized those data[51–53]. An extensive systematic review of treatment of liver metastases identified 43 studies (all retrospective) encompassing 1,686 patients of varying histology, clinical presentation, and sample sizes. Sixty percent were ER positive and 25% were HER2 positive. All underwent liver metastasectomy. Median overall survival was 36 months, five-year survival rate was 37%, and 30-day post-operative mortality was 0.7%[54]. Because this review was limited by extreme heterogeneity in patient population and differing trial designs, we interpret these descriptive analyses with some caution. Still, some interesting nuances emerged on deeper analysis of the trials, including one case control study of 51 patients undergoing concurrent systemic chemotherapy and liver

metastasectomy and 51 matched non-surgery patients. Patients had ≤4 liver lesions and only bone metastases were allowed in addition the liver metastases. Multivariate analysis revealed a 3 fold higher risk of death when surgery was *not* performed[55]. Further, the three-year survival rate was 50% in the non-surgery cohort, and 80% in the surgery cohort. Factors that predicted poor prognosis were >1 course of chemotherapy, and presence of bone metastases. These data do suggest that liver resection has particularly favorable results in the oligometastatic population. In unresectable or high risk surgical patients, alternatives to resection include radiofrequency ablation (RFA) and trans-arterial chemoembolization (TACE)[56–58]. Both forms seem to be relatively safe with low adverse events rates. Head to head trials are lacking, though there is some evidence that the combination appears to be safe and superior to RFA alone[59]. A meta-analysis of 14 studies evaluated the efficacy of RFA compared to hepatic resection and found the latter group to be more efficacious (combined OR for 5 year OS 0.38, p<0.001)[60].

Pulmonary metastasectomy

As with the literature for hepatic resection, there are no high-quality prospective data upon which to base a decision for or against recommending pulmonary metastasectomy. However, several cohort studies and case series have been published with five year overall survival rates ranging from 36% to 62%[61–67]. Pooling the available literature, a recent systematic review and meta-analysis of 16 cohort studies comprising nearly 2,000 patients sought to describe the outcomes of patients undergoing local resection with or without concurrent systemic therapy[68]. All but one were retrospective, and few had follow up longer than five years. Pooled five-year overall survival rate was 46%, and solitary pulmonary metastasis was found to be a significant prognostic factor favoring improved OS (pooled HR 1.30 for OS). It should be noted that the individual study populations, while heterogenous, did seem to be highly enriched for the oligometastatic phenotype in that several studies excluded patients with extra-pulmonary metastases or even bilateral pulmonary metastases. One should also appreciate the fact that many of these studies predated modern radiation techniques and targeted systemic therapy.

Future directions.

It should be readily apparent at this point that there is a paucity of high-quality published data regarding treatment of OMBC. Even the systematic reviews and meta-analyses are limited by the quality and heterogeneity of their individual studies. However, there is reason for optimism. Given increasing awareness and interest in the OM phenotype, several prospective phase II/III randomized controlled trials are underway, evaluating novel treatment strategies for OMBC (see Table 2 for a list of selected ongoing trials utilizing SBRT). A phase III study in the Netherlands (NCT01646034) is assessing the role of high dose chemotherapy with carboplatin, thiotepa, and cyclophosphamide in homologous recombination deficient oligometastatic breast cancer, with the hypothesis that these tumors are particularly sensitive to alkylating agents designed to disrupt double stranded DNA. Multiple trials are evaluating the use of SABR and/or traditional surgery in addition to standard of care systemic therapy in the first line setting for newly diagnosed OMBC (e.g. CLEAR, NCT03750396; STEREO-SEIN, NCT02089100; NCT02364557). A novel pilot

phase I study in Australia is evaluating the role of SABR followed by 6 months of anti-PD1 therapy with pembrolizumab, with a goal of showing both safety and enhanced immune activation (BOSTON-II, NCT02303366). This strategy is of particular interest, given its recent success in lung cancer where a phase 2 single arm study showed a 13-month PFS benefit compared to historical controls in OM non-small cell lung cancer[69]. In diseases other than breast cancer, novel prospective trials are looking to collect detailed genomic data in the form of CTC's, circulating tumor DNA, and circulating T cell repertoires as they relate to site directed therapy, such as the phase II ORIOLE trial in castrate sensitive metastatic prostate cancer[70]. This design would serve as an excellent model for further investigating OMBC. 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. One critical ongoing challenge, however, is the varying definitions of 'oligometastatic' in the inclusion criteria, which ranges from two to five based on the particular trial. To facilitate comparison of trial results and uniformity in future trial designs, it would be prudent to employ a universal definition of 'oligometastatic' within the breast cancer investigative community.

Conclusion

The 'oligometastatic state' has gained increasing visibility and attention as we have come to appreciate the incredibly complex biologic diversity among primary and metastatic tumors. Novel insights into the molecular alterations and unique miRNA expression signatures of oligometastatic disease as compared to polymetastatic disease lends credence to the concept of the oligometastatic state being a unique, distinct entity. Future directions at establishing measurable biomarkers with which we can track the virulence of metastasis will potentially open up new treatment strategies.

With an increasing spotlight on this disease state, data from the first randomized prospective trials in OM are now becoming available. Thus far, increases in PFS and OS in SABR-COMET are promising and we await confirmatory results from phase III clinical trials. However, an improved PFS and even OS do not necessarily equate to 'cure.' And so, the most essential question remains: is oligometastatic disease curable? In the breast cancer population, where a considerable portion of patients are at risk of early recurrence (as in HER2+ and triple negative disease) as well as late recurrence (as in hormone positive disease)[71], answering this question is vital as it may help navigate treatment decisions that have the potential to spare toxicity and still produce long-term remissions.

With the exception of rare case reports and series noting extraordinary durations of response to local treatments[72], there is not yet any consistent data to suggest that oligometastatic disease is truly curable. This may well change in the next decade as prospective randomized controlled trials report their results. Still, the literature to date does make a compelling argument that OMBC behaves more favorably than widespread metastatic disease. One major question the breast cancer community will need to address is whether we can utilize local therapies *in lieu of* systemic chemotherapy up front to prolong progression free survival and extend the totality of treatment options available to our patients while minimizing toxicity. With the pace at which the scientific community is moving to

understand and translate the biology of this disease into human trials, we can only imagine what a review paper in ten years will look like.

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Table 1.

Summary of Radiation Therapy Trials

Author / Year	Disease	Design	Definition	*n* Patients	Intervention	Outcome	Results
Palma D. 2019	Mixed	Prospective, Randomized Phase II	≤5 lesions	99	SABR vs palliative standard of care	Median OS	28mo control vs 41mo SABR
Trovo M. 2018	Breast	Prospective, Single Arm, Phase II	≤5 sites	54	SBRT 30–45Gy or IMRT 60Gy	Primary: PFS Secondary: OS	1yr 75% 2yr 53% 2yr 95%
Scorsetti M. 2018	Mixed	Prospective, Single Arm, Phase II	≤3 liver sites	61	SBRT to liver metastases	Primary: LC Secondary: OS	1yr 94% 3yr 78% 5yr 78% mOS 27.6mo
Milano MT. 2008	Mixed	Prospective, Single Arm	≤5 sites	121	SBRT 5Gy	OS PFS LC DC	2yr OS 50% 26% 67% 34%
Ost, P. 2018	Prostate	Prospective, Randomized Phase II	≤3 lesions	62	Surgery (6) or SBRT (25) vs surveillance (31)	ADT-free Survival	Median 13mo surveillance vs 21mo SBRT/Surgery
Salama 2012	Mixed	Prospective, Single Arm	≤5 Metastases	61	SBRT	OS	1yr 81.5% 2yr 56.7%
Onal C. 2018	Breast	Retrospective	≤5 Metastases	22	SBRT	Local Control Rate OS PFS	2yr 88% 2yr 57% 2yr 8%
Andratschke N 2018	Mixed	Meta-Analysis	≤4 Liver Metastases	474	SBRT	OS 1yr control rate 2yr control rate	Median 24mo 77% 6%
Bhattacharya I. 2015	Mixed	Retrospective	≤3 Metastases	76	SBRT	2yr OS 2yr PFS	63.2% 26.2%
Mahadevan A. 2018	Mixed	Retrospective	Liver metastases (max # not defined)	427	SBRT	OS	Median 22mo *Breast 21mo
Loi M. 2018	Mixed	Retrospective	≤3 Lymph node metastases	91	SBRT	Locoregional RFS Distant Metastasis Free Survival	4yr 79% 4yr 44%
Fumagalli I. 2012	Mixed	Retrospective	≤5 sites	90	SBRT	LC OS DFS	1yr 84.5% 2yr 66.1% 2yr OS 70% mDFS 6.7mo
Rades D. 2018	Breast *spinal cord compression	Retrospective	1–4 vertebrae *no other bony or visceral disease	159	Radiotherapy (not further defined)	LC OS	2yr 87% 2yr 67%

Author / Year	Disease	Design	Definition	*n* Patients	Intervention	Outcome	Results
Yu T. 2019	Mixed	Retrospective	≤5 sites	16	SABR	OS	1yr 84%
Xu L. 2017	Small Cell Lung Cancer	Retrospective	1 organ met or multi-brain mets or continuous vertebral mets covered in 1 XRT field	78	Chemo + XRT (IMRT or AP Field Radiotherapy or 3D Conformal Radiotherapy) Vs Chemo alone	2yr OS 2yr PFS 2yr Local Control Rate	25.2% vs12.7% 19.3% vs 4.8% 57.6% vs 9.6%
Triggiani L. 2017	Prostate Cancer	Retrospective	≤3 lesions in bones or lymph nodes	100	SBRT	Distant PFS ADT-Free Survival	Median 17.7mo Median 20.9mo
Takahashi W. 2012	NSCLC	Retrospective	≤3 metastases	42	SBRT	2yr Local Control Rate 2yr OS rate	87% 65%

Table 2.

Summary of Ongoing Clinical Trials

Principal Investigator	NCT	Disease	Design	Definition	Target Accrual	Intervention	Outcome
Dirix, P.	NCT03486431	Mixed	Prospective, Phase 1	≤3 lesions	99	SABR	Primary: DLT Secondary: Median PFS Local Control Rate
Bourgier, C.	NCT02089100	Breast	Randomized, Phase 3, Multi-Center	≤5 lesions	280	SABR vs best supportive care	PFS
De Rose, F. Comito, T.	NCT02581670	Breast *Lung/Liver Metastases	Non-Randomized Phase II	1–4 Lesions	40	SBRT	Primary: Local Control, Toxicity Secondary: PFS, OS
Chmura, S.	NCT02364557	Breast	Randomized Phase II/III	1–4 Lesions	402	Systemic Therapy +/− SBRT	Primary: PFS, OS Secondary: Presence of CTC (baseline, after treatment); levels of ctDNA; incidence AE's; appearance of new metastases
Khoo, V.	NCT02759783	Breast, Prostate, NSCLC	Randomized Phase II/III	≤3 Lesions	245	Standard of Care +/− SBRT	Primary: PFS Secondary: OS, Local Control, Toxicity