



# SABR in oligometastatic breast cancer: Current status and future directions



Rachel Stewart <sup>a, \*</sup>, Michelle White <sup>b</sup>, Jennifer Tan <sup>a</sup>, Shankar Siva <sup>a, c</sup>, Lama Karroum <sup>a</sup>, Steven David <sup>a</sup>

<sup>a</sup> Department of Radiation Oncology, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria, Australia, 3000

<sup>b</sup> Monash Cancer Centre, 823-865 Centre Road, Bentleigh East, Victoria, 3165, Australia

<sup>c</sup> The Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Victoria, 3010, Australia

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## ABSTRACT

Oligometastatic breast cancer (OMBC) is a heterogeneous disease with intrinsic biological diversity. It is increasingly accepted in clinical practice that patients with OMBC could be treated with the expectation of long-term disease remission. Local ablative treatments, such as radiotherapy or surgery have a role in this setting. At present, patients that may benefit are characterised by low tumour burden, long disease-free interval and the capacity to completely ablate all sites of disease. In the future, biological or genomic classifiers may help predict which patients may benefit the most from local ablative treatments. This review provides an overview of the proposed classifications of oligometastatic disease and outlines the standard systemic treatment options of endocrine therapy, chemotherapy, and immunotherapy. The evidence for localized treatment with stereotactic ablative body radiotherapy (SABR) is presented. We discuss current active trials in oligometastatic cancer and discuss potential future directions for the use of SABR in the treatment of OMBC.

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## 1. Background

Advanced breast cancer represents a heterogeneous group of biological entities. Systemic therapy is the backbone of treatment resulting in improved rates of disease control and overall survival

\* Corresponding author.

E-mail address: [Rachel.stewart@petermac.org](mailto:Rachel.stewart@petermac.org) (R. Stewart).

(OS) [1]. Patients with a low disease burden (oligometastases) and/or long disease-free interval, can be considered for an aggressive approach to eradicate disease. Stereotactic ablative radiotherapy (SABR) as a safe and effective metastasis directed therapy is being increasingly utilised. There is evidence of improvement in progression-free survival (PFS) and OS outcomes for SABR in some cancer subtypes [2–4]. However, due to limited evidence supporting the use of SABR in oligometastatic breast cancer (OMBC), its utility remains confined within the context of clinical trials while the landscape of systemic therapies rapidly evolves.

This review outlines the current state of systemic treatments recommended in the different biological subtypes of advanced breast cancer and summarises the current published data related to SABR in advanced OMBC. This includes the current state of active clinical trials and the potential future directions for the integration of SABR into the management of patients with advanced OMBC.

## 2. Biological subtypes of advanced breast cancer

It is important to appreciate that breast cancer is a heterogeneous disease in order to determine the best strategies for treatment. Each subtype has a unique biology and natural history that must be considered when determining management. Breast cancer subtypes are broadly characterised by their hormone receptor (HR) status and human epidermal growth factor (Her2) overexpression, as this relates to prognosis and response to systemic therapy.

Tumours with expression of either oestrogen receptors (ER) or Progesterone receptors (PR) in at least 1% of tumour cells are considered HR positive [5]. Approximately 70% of breast cancers are HR positive due to their ER status [6]. Approximately 20% of breast cancers overexpress the Her2 oncogene [7]. Finally, approximately 15% of all breast cancers are triple negative (TNBC), meaning they lack expression of the ER/PR and Her2 receptors [8]. TNBC tumours tend to behave in an aggressive way and relapse early, often within 5 years [9]. For metastatic breast cancer, the natural history of these subtypes is quite different with the median survival for TNBC in the range of 10–13 months, Her2 positive in the order of 5 years and ER positive in the range of 4–5 years [10,11]. These significant differences in survival may impact on decision making regarding management of oligometastatic disease and clinicians need to consider this when recommending metastasis directed therapies.

## 3. Current standard of care in metastatic breast cancer

The current standard treatment of metastatic breast cancer is predominantly reliant upon systemic therapies, with choice of therapy directed by the specific biological subtype. Targeted radiation therapy is usually reserved for use in a palliative capacity to alleviate symptoms.

Patients with HR positive and Her2 negative disease are typically treated with endocrine therapy in combination with a CDK 4/6 inhibitor. There are currently three CDK4/6 inhibitors in clinical use: palbociclib, ribociclib and abemaciclib. Clinical trials using these agents have produced very similar results. First line therapy with an aromatase inhibitor (AI) in combination with one of these agents is associated with a median PFS of 24.8 months and overall response rates of 53–59% [12–14]. Fulvestrant is the endocrine therapy of choice in patients who have developed metastatic disease while being treated with an AI [15]. Following the development of resistance to other endocrine based therapies patients are usually recommended chemotherapy.

In patients with HER2 positive disease, standard first line therapy consists of a taxane in combination with trastuzumab and pertuzumab. In the CLEOPATRA trial, using this triplet in the first line setting was associated with a median OS of 56.5 months [16].

The antibody drug conjugate trastuzumab emtansine is frequently used in a second line setting based on data from the Emilia study [17]. Subsequent current lines of therapy would involve using trastuzumab backbone with either chemotherapy agents or endocrine agents in ER positive disease. Multiple new agents are in preclinical or clinical development in the Her2 setting including agents such as trastuzumab-deruxtecan [18] and other drug/antibody complexes.

Historically patients with metastatic TNBC have limited treatment options apart from multiple lines of chemotherapy. More recently new therapeutic options have been identified. Immunotherapy with both atezolizumab and pembrolizumab has been shown to have activity in patients with TNBC whose tumours are programmed death-ligand (PDL) positive. In the Impassion 130 study, patients receiving atezolizumab in conjunction with nab paclitaxel had an improvement in PFS from 5.5 to 7 months (HR 0.62,  $p < 0.0001$ ) and improvement in OS from 15.5 months to 25.0 months (HR 0.45) [19]. In the Keynote 355 study, the addition of pembrolizumab to nab paclitaxel, paclitaxel or carboplatin/gemcitabine resulted in an improvement of PFS from 5.5 months in the chemotherapy alone group versus 9.7 months in the pembrolizumab/chemotherapy group in the PDL1 high group [20]. Other new therapies include Sacituzumab, an antibody-drug conjugate, which has activity in previously treated TNBC including improvements in PFS and overall survival when compared with physician's choice chemotherapy [21]. PARP inhibitors have also demonstrated activity in patients with germline BRCA1/2 mutations based on the result of the Olympiad and EMBRACA studies [22,23]. There does however remain an unmet need in terms of active therapies for patients with metastatic TNBC.

## 4. Oligometastatic disease

By observing the natural history of breast cancer, Hellman and Weichselbaum [24] coined the state of “oligometastases” to describe the existence of a state of limited metastatic burden. Studies have suggested patients with low volume OMBC could expect long-term disease remission or experience improvement in progression-free survival if all the tumour cells can be removed or treated effectively [25–31]. Fig. 1 is the EORTC proposed classification system of different oligometastatic states with different natural histories that may respond best to varying treatment strategies [32]. These include patients who have responded well to systemic therapy but have 1 to 5 resistant lesions (termed “induced oligometastatic disease”) and patients who have no history of polymetastatic disease presenting with oligometastatic (1–5 metastases) disease, termed “genuine oligometastatic disease”. Further sub-categories of oligorecurrence, oligopersistence, and oligoprogression have also been identified. This recognises that variations in disease presentation may in turn represent differences in pathological sub-type.

The biological basis of these oligometastatic states are supported by the pre-clinical evidence that these lesions may represent resistant sub-clones of tumour, resulting in intra-tumour heterogeneity. Modern genomic techniques have confirmed that tumours are admixtures of different populations of tumour cells with differing phenotypes, termed subclones [33]. These subclones exist within discrete areas of tumour masses (intra-tumour heterogeneity), and also are represented in distinct metastatic sites (inter-tumour heterogeneity [34]). Treatment is known to impose a strong selective pressure on tumour subclonal structure, with the phenomenon of acquired resistance (progression after an initial response) generally arising from break-out of a restricted set of subclonal populations resistant to the current therapy [35,36]. By eradicating these resistant subclones, it is hypothesised that the

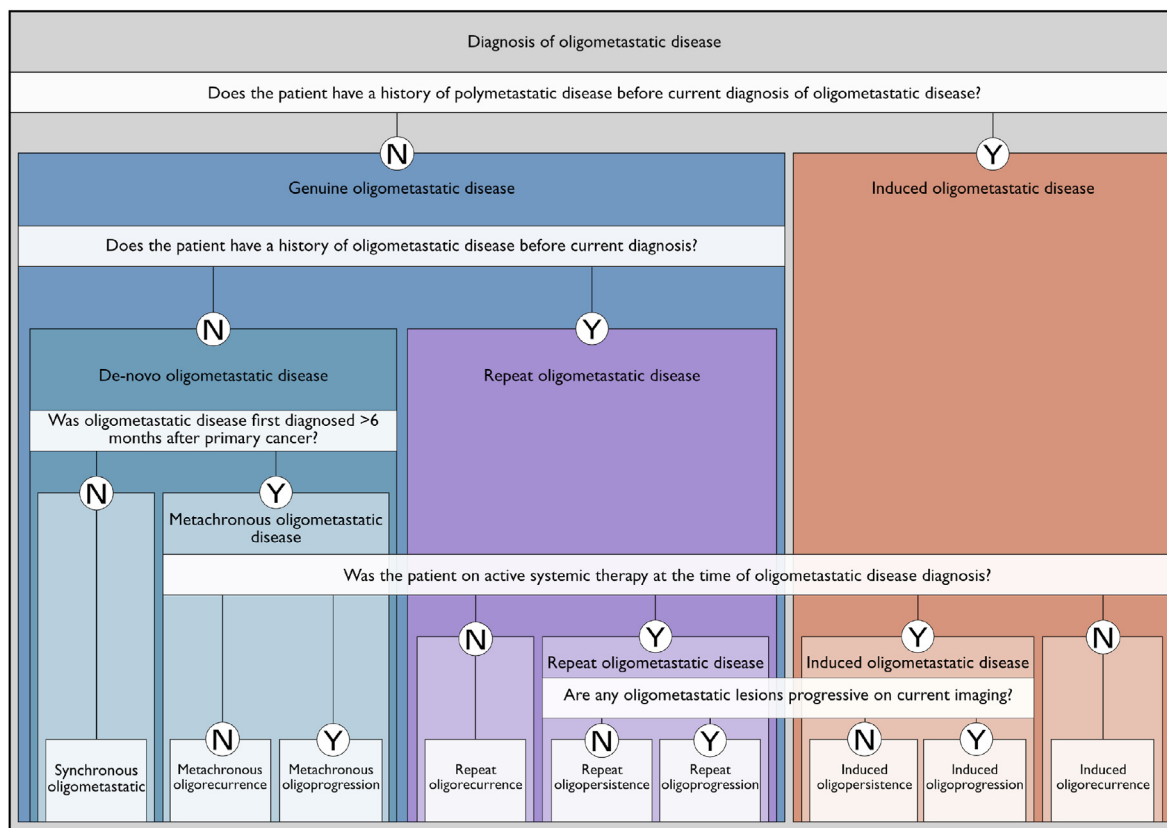


Fig. 1. The EORTC proposed classification system of different oligometastatic states.

efficacy of systemic therapies can be maintained, and the development of more widespread disseminated disease can be restricted.

Coleman et al. observed that patients with bone only disease have a longer survival than patients with visceral metastases – up to 20% alive at 5 years [37], with a median survival of over 72 months in selected patients [38,39]. Therefore, durable local control of bone metastases is increasingly recognised, and in selected patients, local ablative therapy can be considered.

### 5. Surgical intervention of oligometastatic breast cancer

Several trials have reported on the surgical approach to eradicate discrete metastasis with resistant subclones. These trials have yielded varied results but have shown enough promise to warrant further consideration of a more integrated approach to treatment of oligometastatic disease.

Yoshimoto et al. [29], reported retrospectively on the effects of resecting solitary lung metastases as an adjunct to standard of care systemic therapies. The study included 90 women with solitary lung metastases from primary breast cancer. Of the group, 85 women had lung as the first site of recurrence, 4 were in remission from loco-regional spread to skin or lymph nodes, and 1 had stage IV lung metastases. The mean age was 55.1 years and mean disease-free interval (DFI) before recurrence was 5.6 years. The study found a significantly increased cumulative 10-year survival rate of 40% for the 90 patients who had undergone surgery, compared to a 10-year survival rate of only 6.5% in a group of 312 similar women who had been treated with chemotherapy and hormonal therapies alone. The most pertinent factors influencing survival rates were the

patients' DFI and stage at the time of breast surgery or diagnosis. A DFI greater than 3 years was a significant positive prognostic factor with a 10-year survival rate of 47%. Unsurprisingly, patients with stage I disease at diagnosis had more favourable outcomes with a 10-year survival rate of 74%. Post-operative complications were reported, including infection, atelectasis, and hepatitis due to transfusion. There was also 1 death related to surgery.

In a systematic review conducted by Chua and colleagues the benefits of surgical resection of hepatic metastasis from breast cancer was assessed [30]. Across 19 studies, comprising a total of 553 patients, they looked at mortality, morbidity, median OS, 5-year survival, and prognostic factors as primary outcome measures. For patients who had undergone hepatectomy for metastatic lesions, median overall survival was 40 months (range of 15–74 months) and the median 5-year survival rate was 40% (range of 21–80%). The postoperative complication rate was 21% (range of 0–44%), however the severity and nature of these complications was not reported. In contrast to the trial by Yoshimoto et al. no significant association was shown between survival and stage of primary tumour, lymph node involvement, or number and size of liver metastases.

These studies support the role of surgical metastasectomies in selected patients with positive impact on survival. However, surgery itself is not without risks and can result in significant post-operative morbidity. The safest and most reliable method of treating oligometastatic disease is yet to be established. The authors propose Stereotactic Ablative Body Radiotherapy (SABR) as an attractive non-invasive low morbidity option to bridge the gap between effective removal of suitable metastatic lesions and minimising treatment related morbidity.

## 6. Stereotactic ablative body radiotherapy

The term stereotaxis describes any technique utilising internal imaging to localise and target an internal anatomic structure. Stereotactic ablative body radiotherapy (SABR), also known as stereotactic body radiotherapy (SBRT), refers to the use of stereotactic techniques to accurately direct radiation beams to a desired extracranial site. This is achieved with a co-ordinated system using combinations of sophisticated internal imaging, advanced technologies capable of producing highly conformal beam arrangements, and patient immobilisation. SABR allows for the delivery of high dose ablative radiotherapy in only one to five treatments, as opposed to conventionally fractionated radiotherapy which requires increased fractionation regimens to reach an effective dose while minimising toxicity [40,41]. It is specifically noted that stereotactic radiosurgery (SRS) is the term commonly used to describe treatment of an intracranial target, hence treatment of intracranial lesions has generally been excluded from the studies put forth in this review.

SABR is an emerging tool for metastasis-directed curative intent therapy, which has proven to be safe and feasible in treating oligometastatic disease of various tumour types [2]. There is a paucity of prospective evidence supporting its use in breast cancer but is gaining traction, within and beyond clinical trials. We reviewed the published literature to date, the current state of active clinical trials and the potential for future research to help inform how to integrate SABR into clinical practice in the era of modern systemic therapies.

There now exists randomised evidence of an overall survival benefit with the use of SABR in the treatment of oligometastatic disease. In 2019 a phase 2, randomised-controlled trial aimed at assessing outcomes of standard of care palliative treatments with versus without SABR in patients with up to 5 metastatic lesions where the primary tumour is controlled [2]. This was a multinational study conducted across 10 hospitals in Canada, The Netherlands, Scotland, and Australia. It included 99 patients (18% of whom had primary breast cancer) randomised in a 1:2 ratio to either standard of care palliative treatment with or without SABR. Initial findings saw an increase of 13 months in median OS, as well as a doubling length of PFS, in patients who received SABR. However, higher rates of treatment related toxicity were seen in the SABR group (including 3 deaths) compared to the control group. Subsequent long-term follow up demonstrated a significant difference in 5-year OS of 42.3% in the SABR arm versus 17% in the control arm. While 5-year PFS in the SABR arm was 17.3%, this endpoint was not reached amongst the controls. Despite the early discrepancy in rates of toxicity between groups, no detrimental long-term effect on quality of life was found.

Specific patients with OMBC were evaluated in a prospective phase II trial lead by Trovo [3]. This included a total of 54 patients, 40 of whom had oligometastatic disease at diagnosis, and 14 of whom had induced oligometastatic disease following systemic therapy. Sites of disease were predominantly bone, followed by lymph nodes, then liver and lung. Analysis of the primary endpoint, PFS, was positive with a 1-year PFS of 75% and 2-year PFS of 53%. Results on secondary endpoints of local control, OS, and toxicity were encouraging. At 2 years the local control rate was 97% and OS rate was 95%. No toxicities of grade 3 or higher were reported. Interestingly, no significant difference in PFS was seen between patients who had induced oligometastatic disease versus those with de novo oligometastatic disease, nor was there a significant difference between those who had metastases at diagnosis compared to those who had progressed to an oligometastatic state. The number of metastatic lesions was not associated with PFS, however 85% of patients had only 1 or 2 metastases. Despite 80% of

patients having ER positive disease, the large majority received chemotherapy alone as their systemic treatment. This raises the possibility that the results of this study could be attributed to the intensity of systemic treatment, rather than the addition of SABR targeting discrete metastatic lesions.

The effectiveness of SABR in achieving long term control of bony oligometastatic lesions in patients with breast cancer was seen in a prospective interventional trial by David et al. [42]. In this study 15 breast cancer patients, each with 1–3 metastatic lesions to bone and a controlled primary, were treated with a single fraction of 20Gy to all visible sites of disease. The median age of participants was 63 years, the majority of whom (9 patients or 86%) had hormone receptor positive disease. Using this single fraction regimen treatment with SABR was very well tolerated. Even though 14 patients (93%) reported some radiotherapy related side effects, none were of grade 3 or higher. The most common adverse effect attributed to SABR was grade 1 bone and back pain. Excellent rates for local control of disease were seen in this study with 100% local PFS at 2 year follow up. Distant PFS was also high, at 67% (10 patients), 8 of whom had HR positive disease and did not require a change from endocrine therapy as their only form of systemic treatment. This observation suggests that, in patients who have otherwise shown response to endocrine therapy, SABR has the potential to delay, or even eliminate, the use of more toxic systemic treatments, including chemotherapy. This could have a significant impact on quality of life.

Milano et al. analysed two prospective pilot studies, the first included only patients with primary breast cancer, the second included all primary cancers [43]. In 2012 they published the results of long-term follow up [4]. They reported on 39 breast cancer patients, out of a total 121 cancer patients, focussing on those who received curative intent SABR for oligometastatic disease. It was found that the breast cancer patients had significantly higher rates of OS (OS) and freedom from distant metastases (FFDM). The 6-year OS and FFDM rates in this group were 47% and 36% respectively, compared to only 9% and 13% in non-breast cancer patients. For OMBC, bone metastasis was associated with a greatly reduced risk of death (HR 0.24,  $p$  0.057). This may play a role in the increased survival rates of breast cancer patients when compared to non-breast cancer patients since a much higher portion of them, 28% compared to 5% respectively, had bone involvement. In addition, this study demonstrated the safety of SABR treatment. There were no cases of grade 4 or 5 toxicities. This study suggests SABR as an adjunct to systemic therapies could be effective, particularly in patients with bone-only OMBC. Future assessment of favourable and unfavourable prognostic patient factors for this subset of patients are a work in progress.

### 6.1. SABR for the palliative treatment of spinal metastases

While the studies discussed above focus on the use of SABR with curative intent or with the aim of overall disease control in oligometastatic cancer, there is also interest in exploring the benefits of SABR in the palliative setting, particularly in the management of spinal metastases.

SABR using CyberKnife technology (manufactured by Accuray, California, USA) has been utilised to treat spinal metastatic lesions [44,45]. In one study 18 women with histologically confirmed spinal metastases from breast cancer treated with Cyberknife were compared with 18 matched patients who received conventional external beam radiotherapy [44]. Follow up at 24 months found no difference between the groups with respect to ambulatory levels, performance score, or pain levels. Results show a slightly improved survival rate and lower toxicity rate in the Cyberknife cohort, however neither of these were statistically significant.

Cyberknife was also utilised in a prospective evaluation of 50 women with spinal metastases from breast cancer, 48 of whom had previously undergone external beam irradiation to the spine preventing further conventional radiotherapy treatment [45]. The aim of this study was to assess the safety of SABR for spinal metastatic lesions at similar doses to those used for intracranial stereotactic radiosurgery. Side effects were minimal with no cases of symptom exacerbation, haemorrhage, or new neurology in the immediate treatment period, as well as no cases of radiation induced myelopathy or radiculopathy on follow up. In addition, stereotactic treatment was seen to be efficacious for both long term pain control and long-term radiographic control.

The efficacy of SABR in palliative treatment of spinal metastases has also been demonstrated by Sahgal et al. in a randomised phase II/III study comparing conventional radiotherapy (CRT) to stereotactic body radiotherapy (SBRT) [46]. A total of 229 patients were enrolled, 115 of whom received CRT to a dose of 20Gy in 5 fractions. The other 114 participants were treated with SBRT to a dose of 24Gy in 2 fractions. Patients in the SBRT arm of the trial experienced a higher rate of pain relief at both three and six months compared to the CRT arm. The primary endpoint measured was complete response (CR) for pain at three months. This was achieved by 14% (16 of 115) of patients who were treated using CRT, compared to 36% (40 of 114) of patients treated with SBRT. Durability of response was also seen with similar rates of CR at 6 months in each group, 16% in the CRT group versus 33% in the SBRT group. In addition, there were fewer incidences of post-radiation vertebral compression fractures, and 0 versus 2 (2%) cases of progression to malignant spinal cord compression, in the SBRT arm compared to the CRT arm respectively. Higher rates of site specific progression free survival were also seen in patients treated with SBRT, and rates of adverse events were similar in each cohort.

## 7. Actively recruiting clinical trials

Table 1 lists the trials specific to recruitment of patients with breast cancer, receiving SABR. Two large, randomised trials have PFS (in addition to OS for the NRG trial) as the primary endpoint and are comparing the standard of care with or without SABR used to treat all sites of oligometastatic disease, with neither trial specifying biological subtype. AVATAR is a more specific study, attempting to study impact of SABR on all sites of oligoprogressive disease in patients with ER positive, Her-2 negative breast cancer.

**Table 1**  
Trials with eligibility specific to breast cancer.

Trial name	Design	Recruitment target	Primary outcome	Sponsor
Stereotactic Body Radiotherapy (SBRT) for the Treatment of Oligometastasis in Breast Cancer Patients (STOMP): A Prospective Feasibility Trial [47]	Phase I feasibility study	n = 30	Technical feasibility of planning SBRT to multiple sites	Juravinski Cancer Center
Trial of Superiority of Stereotactic Body Radiation Therapy in Patients with Breast Cancer (STEREO-SEIN) [48]	Randomised Multicentric Phase III trial	n = 280	PFS	Gustave Roussy, Cancer Campus, Grand Paris
Study on SBRT for Inoperable Lung and Liver Oligometastases From Breast Cancer [49]	Prospective non-randomised phase II study	n = 58	Toxicity and Local Control	Istituto Clinico Humanitas
Standard of Care Therapy With or Without Stereotactic Radiosurgery and/or Surgery in Treating Patients With Limited Metastatic Breast Cancer [50]	Randomised phase IIR/III Trial	n = 402	PFS and OS	NRG Oncology
Local Treatment in ER-positive/HER2-negative Oligo-metastatic Breast Cancer (CLEAR) [51]	Multi-centre, single-arm, phase II trial	n = 110	PFS	Gangnam Severance Hospital
Stereotactic Radiotherapy for Oligoprogressive ER-positive Breast Cancer (AVATAR) [52]	Multicentre phase II registry-based study	n = 32	Time to change in systemic therapy	Peter MacCallum Cancer Centre
Metastases-directed Radiotherapy in Addition to Standard Systemic Therapy in Patient with Oligometastatic Breast Cancer (OLIGOMA) [53]	Randomised controlled multi-national, multicentre therapeutic confirmatory trial	n = 564	PFS and quality of life	University Hospital Schleswig-Holstein

Challenges may exist for investigators in recruiting adequate numbers to a study specific to a small sub-group of patients.

Table 2 lists trials that are inclusive of, but not specific to, patients with oligometastases from breast cancer. There are two trials from Memorial Sloan Kettering, both randomised phase II trials with PFS as the primary endpoint specifically limiting recruitment to patients with either TNBC or NSCLC and comparing standard of care to the addition of SABR, however one trial specifically addresses the question of oligoprogressive disease by limiting recruitment to patients that are progressing in 1–5 metastatic sites. The randomised trial comparing standard of care to the addition of SABR to all sites of oligometastases across patients with breast, NSCLC and prostate cancer (STEREO-OS) limits recruitment to patients with 1–3 bone only oligometastases, presumably a more indolent disease subtype.

### 7.1. SABR and immunotherapy

There is a growing area of research studying the potential synergistic effects between SABR and immunotherapy. It is hypothesised that the use of targeted radiotherapy together with immune checkpoint inhibitors may have a complementary effect, triggering an innate host immune response. This not only has the potential to enhance the short-term capabilities of immunotherapy in eradicating cancer, but introduces the possibility of inducing a long lasting anti-cancer immunity against a patient’s own tumour cells [61]. At this time, developments on this topic area have been predominantly pre-clinical, however this is an emerging area with exciting potential with some trials already showing promise with regard to breast cancer [62,63].

### 7.2. Future directions

It is becoming more evident that oligometastatic and poly-metastatic disease may have different biology and could be considered separate disease entities, hence more tailored approaches to treatment should be developed [19]. We await future phase 3 trials to gain a strong evidence base to determine what the most efficacious management pathways are while maintaining low toxicity rates and high tolerability. Further to this, there needs to be more focus on breast cancer specifically as a heterogenous disease that will respond best to various therapies.

Utilisation of biologic and genomic classifiers as a strategy to

**Table 2**  
Trials with eligibility not specific to breast cancer.

Trial name	Design	Recruitment target	Primary outcome	Sponsor
Stereotactic Body Radiation for Spinal Metastases in Favorite Tumors [54]	Phase II study	n = 100	The rate of relieved pain	Renji Hospital
Randomized Study of Stereotactic Body Radiation Therapy (SBRT) in Patients With Oligoprogressive Metastatic Cancers of the Breast and Lung [55]	Randomised, phase II trial	n = 160	PFS	Memorial Sloan Kettering Cancer Center
Standard Treatment ± SBRT in Solid Tumours Patients With Between 1 and 3 Bone-only Metastases (STEREO-OS) [56]	Randomised, Phase III trial	n = 196	PFS	UNICANCER
Conventional Care Versus Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases (CORE) [57]	Multi-centre phase II/III randomised controlled trial	n = 245	PFS	Royal Marsden NHS Foundation Trust
Stereotactic Body Radiation Therapy in Treating Patients With Metastatic Breast Cancer, Non-small Cell Lung Cancer, or Prostate Cancer [58]	Phase I study	n = 42	Dose limiting toxicity	NRG Oncology
Investigating the Effectiveness of Stereotactic Body Radiotherapy (SBRT) in Addition to Standard of Care Treatment for Cancer That Has Spread Beyond the Original Site of Disease [59]	Randomised Phase II study	n = 142	PFS	Memorial Sloan Kettering Cancer Center
A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4–10 Oligometastatic Tumours (SABR-COMET 10) [60]	Randomised Phase III study	n = 159	OS	David Palma

predict which patients will benefit most from SABR could be another step towards achieving individualised management of OMBC. At present the Oncotype DX Breast Recurrence Score, a 21-gene assay, is indicated as a prognostic tool in early hormone receptor-positive, HER2-negative breast cancer [64]. Similar genomic testing of oligometastatic lesions has the potential to aid management decisions when considering systemic and local ablative therapies in patients with OMBC.

Future trials are required to investigate the most appropriate treatment methods considering not only the diverse biological subtypes of breast cancer, but also the range of oligometastatic classifications as there are potential variations in outcome based on each of these factors. Integrating SABR with systemic therapies has shown a lot of promise in the treatment of OMBC. The current evidence points towards a positive outcome when utilising SABR in conjunction with systemic therapies, hence this needs to be considered in future studies. An example of this is the AVATAR trial [65] which will build upon the evidence suggesting that SABR can be used alongside systemic therapies to delay progression and increase overall survival, while taking into account the specific biological subtypes and oligometastatic status of patients with breast cancer.

The ideal timing of SABR in relation to systemic therapies is also unknown. Further assessment of the optimal time at which to integrate local ablative therapies (LAT) is warranted. While studies of oligometastatic disease not specific to breast cancer suggest upfront LAT to be efficacious, the potential benefits of a consolidative approach are also recognised [66]. Introducing LAT after a period of systemic therapy would allow for an assessment of response to treatment. This in turn could assist in differentiating patients with truly oligometastatic disease who may benefit from SABR, versus those with subclinical micrometastases who are bound for disease progression. Currently, at least one open randomised trial is recruiting patients for LAT at different times during systemic treatment [50], however this is not specifically considering time at which LAT is introduced when assessing outcomes. Dedicated studies are required to sufficiently determine the timing that will result in the greatest success when treating OMBC.

## 8. Conclusions

Breast cancer is becoming increasingly recognised as a heterogeneous disease which is best treated with a tailored approach. While systemic therapies remain the mainstay of treatment, wider acceptance of the biological diversity between breast cancer subtypes is making way for a broader range of management strategies. Targeted eradication of such groups of resistant subclones, presenting as oligometastases, can lead to increased overall survival in patients with breast cancer. There is a growing body of evidence to support the use of SABR in this setting. Recent studies demonstrate it is safe and effective with the possibility of offering a cure when treating OMBC. Benefits also lie where escalation in systemic therapies could be deferred or delayed. Despite a small number of promising studies, the evidence for SABR as an adjunct to systemic therapy is lacking. We eagerly await the results of active studies, to further clarify the precise role of SABR in advanced OMBC.

## Declaration of competing interest

Rachel Stewart, Michelle White, Jennifer Tan, Shankar Siva, Lama Karroum, and Steven David declare they have no conflict of interest to declare in association with the subject matter of this manuscript. Ethical approval was not required for this review article.

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