The Breast 59 (2021) 144–156

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Diagnosis, biology and epidemiology of oligometastatic breast cancer

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ARTICLE INFO

Article history:
Received 19 November 2020
Received in revised form
31 May 2021
Accepted 23 June 2021
Available online 1 July 2021

Keywords:
Oligometastatic breast cancer
Definition
Biology
Incidence
CTCs
Observatory

ABSTRACT

Does oligometastatic breast cancer (OMBC) deserve a dedicated treatment? Although some authors recommend multidisciplinary management of OMBC with a curative intent, there is no evidence proving this strategy beneficial in the absence of a randomized trial. The existing literature sheds little light on OMBC. Incidence is unknown; data available are either obsolete or biased; there is no consensus on the definition of OMBC and metastatic sites, nor on necessary imaging techniques. However, certain proposals merit consideration. Knowledge of eventual specific OMBC biological characteristics is limited to circulating tumor cell (CTC) counts. Given the data available for other cancers, studies on microRNAs (miRNAs), circulating tumor DNA (ctDNA) and genomic alterations should be developed Finally, safe and effective therapies do exist, but results of randomized trials will not be available for many years. Prospective observational cohort studies need to be implemented.

Contents

Abbreviations: CT scan, Computed Tomography scan; CTCs, circulating tumor cells; ctDNA, circulating tumor DNA; ^{18}F-FDG-PET/CT, Positron Emission Tomography/Computed Tomography with ^{18}fluorodeoxyglucose; ^{18}F-FES, 16α-[^{18}F]-Fluoro- 17β-estradiol; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, Metastatic Breast Cancer; MRI, Magnetic Resonance Imaging; OMBC, oligometastatic breast cancer; OMD, oligometastatic disease; NA, not applicable; NED, No Evidence of Disease; OS, overall survival; RFS, relapse-free survival; SBR grade, Scarf-Bloom-Richardson grade; SBRT, Stereotactic Body Radiotherapy; WB-MRI, Whole-body MRI.

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https://doi.org/10.1016/j.breast.2021.06.010

1. Introduction

Localized breast cancer, unlike metastatic breast cancer, benefits from standardized curative treatment options. But 20–30% of localized breast cancers will have distant relapses, and 4–6% of breast cancers are initially metastatic [1–3]. Metastatic breast cancer median survival is around two to three years [4,5], but long-term survivors have been observed via rare, long-term longitudinal follow-up studies [6]. In a retrospective analysis of 1581 patients treated for metastatic breast cancer, 3.1% were in complete remission five years after diagnosis, and 1–2% were in complete remission at 10 years [7]. In another retrospective analysis of 1045 patients, 75 were in complete remission after a first line of systemic treatment, 28 were alive at a median follow-up of 72 months, and of these, 18 had no evidence of relapse. A small proportion was alive after 15 years [8]. Some of these patients had a limited number of metastases, defined as OMBC.

The concept of OMBC is supported by the idea that this cancer is a biological entity, falling —from a biological point of view— between localized and polymetastatic breast cancer, and that as such, it deserves specific management [9,10]. To confirm this hypothesis, it is necessary to explore the pathophysiological mechanisms that distinguish OMBC from polymetastatic breast cancer, to evaluate the surgical, image-guided and radiotherapy techniques available and to set up prospective trials confirming, or not, the benefit of personalized therapeutic strategies.

Our objective is to provide teams wishing to work on this subject with a synthetic overview of the available data on this subject. It thus appears important for us to know whether the OMBC incidence found in the literature is relevant in designing future clinical trials. For the same reason, it is essential to examine the definitions now available of both OMBC and metastatic sites and to propose standardization of diagnostic imaging. The fact that OMBC has its own specific biology is central to this concept, making us believe it essential to determine what is —and is not— known. We will then show that fragmentary knowledge about OMBC, current recommendations for optimal OMBC care and rapid progress in overall care for breast cancers make implementation of randomized OMBC studies difficult to implement.

In conclusion, recommendations are made for improving knowledge of OMBC to obtain the most robust scientific evidence supporting the benefits of curative strategies.

2. Materials and methods

The first step consisted in reviewing the literature on diagnosis,

definition, and biology of OMBC in PubMed, using Boolean algorithms with no language restriction. We searched for systematic reviews, reviews, clinical studies, imaging, biological and treatment studies related to OMBC.

Clinical trials were eligible when they described original series of patients treated with intention-to-cure in a multidisciplinary strategy including focal treatment of all disease sites (See Table 1). On the other hand, to optimally specify the distribution of the number of metastases and the organs involved at diagnosis, publications were rejected that related to one or two specific organs and those including patients with exclusive local relapse. Systematic reviews were useful to provide information about prognostic factors, efficiency and tolerance of focal treatment by surgery, radiotherapy and image-guided techniques. Certain systematic reviews of non-breast-cancer metastasis treatment were also included for their data on toxicity and local control, possibly applicable to metastatic breast cancer. Both reviews and systematic reviews provided additional relevant references. Our methodology is detailed in Appendix 1.

3. Results

3.1. OMBC diagnosis

Implementing biological studies and clinical trials on OMBC requires homogeneous cohorts of patients and an unequivocal definition of the disease itself. This definition includes not only the concept of oligometastatic cancer, but also of metastatic sites or lesions. It is also essential to harmonize imaging techniques, since their sensitivity and specificity play an indispensable role in counting lesions.

3.2. Clinical definitions

We looked for definitions of OMBC in the literature, whether in guidelines or in clinical studies. We then analyzed the differences found in their quantitative parameters —maximum number of metastases and organs involved—, along with the scientific arguments justifying the choice of these parameters. Since the choice of a cut-off for the number of metastases or the number of organs affected still remains arbitrary, we sought to determine whether certain thresholds were more relevant than others.

To do so, we first reviewed publications related to OMBC multidisciplinary curative treatments (Table 1). In these publications, OMBC definitions invariably include the maximum number of metastases and in some cases their maximum size, as well as the number of organs involved. The maximum number of metastases varies from one to five, but for those studies setting the threshold at three to five, the number of patients meeting the maximal threshold is low. In two studies, the threshold is five and the number of patients at the maximal limit is, respectively, 2% and 8% [11,12]. In one series with a cut-off of three, only 2% of patients reach that threshold [13].

As for the maximum number of organs affected, three studies specify no criterion [12,14,15]. Two others limit inclusion criteria to one affected organ [13,16]. Finally, in three others whose inclusion criteria set no limit to the number of organs involved [11,17,18], the proportion of patients with more than one affected organ varies from 16 to 41%.

All patients included in these studies were selected for the feasibility of focal treatments and thus do not reflect the natural pattern of dissemination in OMBC. Consequently, it was interesting to analyze two publications concerning observational retrospective series of unselected patients not necessarily treated with a curative intent. The first included 131 patients treated consecutively from January 2014 to December 2017. In this cohort, patients were considered to have OMBC when they had one to five disease sites. When either the primary tumor or local relapse was present, they were considered to be a disease site and included in the count. Of these 131 patients, 78% had one or two metastases, and 92% had only one organ involved. None had more than two organs involved [19]. In the second series of 1200 patients treated from 2007 to 2012, 93.6% had one to four metastases. The outcomes differed significantly, with 33.7% patients having multiple metastatic sites [20].

In the end, five metastases appear to be a relevant cut-off point. Among all publications with a threshold of five or more, a lower proportion of patients had a maximum number of metastases (four or five) compared to one to three. An optimal threshold is difficult to determine, however, for the number of organs involved. Some series show that the proportion of patients with more than two organs involved is low, while others report a much higher percentage but with no specification as to whether the primary tumor or a local relapse is included in the organ count.

As for OMBC definitions proposed by learned societies, the European School of Oncology and the European Society for Medical Oncology (ESO-ESMO) Task Force have defined oligometastatic disease as follows: OMBC is *"(…) low-volume metastatic disease with limited number and size of metastatic lesions (up to five and not necessarily in the same organ), potentially amenable for focal treatment, aimed at achieving a complete remission status.*" [21]. The European Society for Radiotherapy and Oncology (ESTRO), together with the American Society for Radiation Oncology (ASTRO), published a consensus document confirming the importance of standardization for oligometastatic disease (OMD) [22]. The document proposes the following definition: "*OMD can to date be defined as: 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be safely treatable*". The ESO-ESMO and ESTRO-ASTRO definition combine an anatomical description with the possibility and choice of implementing therapeutic strategy with a curative intent.

On the other hand, the National Comprehensive Cancer Network (NCCN) [23,24], Arbeitsgemeinschaft Gynakologische Onkologie (AGO) [25], National Institute for Health and Care Excellence (NICE) [26], Japanese Breast Cancer Society Clinical Practice (JBCSCP) [27] and Pan-Asian adapted ESMO Clinical Practice Guidelines [28] give no recommendations on OMBC.

^{18}F-FDG-PET/CT: Positron Emission Tomography/Computed Tomography with ^{18}fluorodeoxyglucose; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MBC: Metastatic Breast Cancer; MRI: Magnetic Resonance Imaging; NA: not applicable; NED: No Evidence of Disease; OMBC: oligometastatic breast cancer; SBR grade: Scarf-Bloom-Richardson grade; SBRT: Stereotactic Body Radiotherapy.

3.2.1. Oligometastatic, oligorecurrent and oligoprogressive breast cancer

The OMBC concept covers three different situations:

- *de novo* OMBC: patients with limited-extent disease at initial diagnosis
- Oligorecurrent breast cancer: patients with initially localized breast cancer that later relapses into an oligometastatic mode [29–31].
- oligoprogressive breast cancer: "*patients receiving systemic therapy who initially demonstrate response of all metastases to systemic therapy and subsequently experience progression in a limited number of disease sites while the rest remain controlled*" [31].

Table 1
Trials involving OMBC with multi-organ intention-to-cure treatment.

Author [reference]	Study period	Study Design	Number of patients	Anatomic inclusion criteria	Recurrent/*de novo*	Imaging tools	Number of organs involved distribution	Number of metastases distribution	SBR Grade	Surrogate Intrinsic Subtypes
					OMBC				HR and HER2 receptors	
Milano [11]	2001 −2011	Monocentric prospective study	48	1−5 oligometastases 1−3 organs No brain metastases	*De novo*: 86% Recurrent: 14%	NA	1 organ: 80% 2 organs: 18% 3 organs: 2%	1 metastasis: 40% 2 metastases: 31% 3 metastases: 15% 4 metastases: 6% 5 metastases: 8%	NA	NA
Trovo [12]	2012 −2015	Prospective Phase II multicentric trial	54	≤5 metastases No brain metastases Primary tumor controlled	*De novo*: 24% Recurrent: 76%	^{18}F-FDG-PET/CT MRI for liver metastases	NA	1 metastasis: 50% 2 metastases: 35% 3 metastases: 11% 4 metastases: 2% 5 metastases: 2%	HR positive: 80% HR negative: 20% HER2 positive: 21% HER2 negative: 79% Grade I: 6% Grade II: 38% Grade III: 56%	Luminal A/B: 80% HER2-Enriched: 7% Triple negative: 13%
Hanrahan [16]	1974 −1992	Phase II, single arm single center	67	1 metastasis	Relapse with NED after local therapy for metastases Recurrent	(Chest X-ray, isotope bone scan, computed tomography scan of abdomen and other areas if appropriate),	1 organ: 100%[a]	1 metastasis: 100%[a]	HR positive: 62% HR negative: 38% HER2 positive: 35% HER2 negative: 54%	NA
Bojko [13]	1995 −2001	Prospective Phase II multicentric trial	48	≤3 metastases 1 organ one-dimensional measurable disease	Both	NA	1 organ: 100%[a]	1 metastasis: 77% 2 metastases: 21% 3 metastases: 2%	HR positive: 52% HR negative: 46%	NA
Kobayashi [17]	1980 −2010	Monocentric retrospective study	75	1 or 2 organs ≤5 metastases per organ	Both	NA	1 organ: 59% 2 organs: 41%	Not described	HR positive: 64%	Luminal A: 35% Luminal B: 9%

(*continued on next page*)

Table 1 (*continued*)

Author [reference]	Study period	Study Design	Number of patients	Anatomic inclusion criteria	Recurrent/*de novo*	Imaging tools	Number of organs involved distribution	Number of metastases distribution	SBR Grade	Surrogate Intrinsic Subtypes
					OMBC				HR and HER2 receptors	
									HR negative: 36%	
				≤5 cm			3 organs or more: 0%		HER2 positive: 17%	HER2-Enriched: 17%
				No encephalic met					HER2 negative: 73%	Triple negative: 24%
Nieto [15]	1991 −1998	Phase II, single arm	60	Limited MBC	Both	Computed tomographic scans of the head, chest, abdomen, and pelvis; bone scan;	NA	1 metastasis: 80%	HR positive: 56%	NA
		single center		Limited bone marrow infiltration (<5%) Chest wall, No liver or encephalic				2 and more metastases: 20%	HR negative: 44% HER2 positive: 39% HER2 negative: 61%	
									Grade I/II: 50% Grade III: 50%	
Yoo [18]	2004 −2008	Retrospective monocentric cohort	50	≤5 metastases	Recurrent	NA	1 organ: 84%	1 metastasis: 62%	HR positive: 80%	
				No brain metastases			2 organs ore more: 16%	2 metastases or more: 38%	HR negative: 20% HER2 positive: 22.9% HER2 negative: 77.1%	
Cha [14]	1993 −2013	Retrospective	49	≤2 metastases	Recurrent > 1 year	Bone:	NA	NA	HR positive: 100%[a]	
		multicentric cohort		1 organ		^{18}F-FDG-PET/CT and MRI			HER2 negative: 100%[a]	
				≤3 cm		Others: various modalities			Grade I: 11/49	
				HR positive/HER2 negative					Grade II 22/49 Grade III 16/49	

[a] Inclusion criteria.

3.2.2. Definition of a metastatic site

The definition of a metastatic site, or lesion, must be clarified. In many studies, it is defined by a single tumor location. In others, it is an affected organ regardless of the number of metastases present therein [32].

Kelly et al. have proposed a definition to calculate the number of metastatic sites: "*For lesions in the brain, bone, lung, and liver, each radiologically identifiable lesion was considered one site of disease. For lesions in the lymph nodes, radiologic involvement of each echelon of the axillary, cervical, or mediastinal lymphatics was considered a single site of disease, even if there were multiple nodes noted in a given echelon. Lesions in or on the ipsilateral breast or chest wall were considered a single site of disease, even when multiple lesions were visible radiographically or clinically. Leptomeningeal disease, malignant pleural effusions, and cutaneous involvement outside the ipsilateral breast or chest wall were considered diffuse disease*". A few complementary points still need to be specified, for example, the qualification of contralateral lymph node involvement, in particular for axillary nodes where there is no primary tumor [33].

3.2.3. OMBC diagnostic imaging techniques

As long as OMBC diagnosis is based on disease burden only — the number of metastases and organs involved — and not on biology, imaging tools will be a cornerstone for OMBC research and management. Indeed, the sensitivity and specificity of imaging techniques for breast cancer staging influences size, location and the number of metastatic lesions observed [10]. And the choice of imaging techniques employed for staging also contributes to the feasibility analysis of focal metastasis treatments.

Among the eight studies presented in Table 1, three give no details about imaging tools used for initial staging [11,13,18]. One of the five remaining studies gives information about the routinely used protocol for exploring metastatic sites — liver Magnetic Resonance Imaging (MRI) and Positron Emission Tomography/Computed Tomography with ^{18}fluorodeoxyglucose (^{18}F-FDG-PET/CT) [12]. A second study reports on a protocol used only for bone metastases quantification [14]. The last three studies describe imaging tests used, but without specifying whether they were part of a predefined protocol [15–17]. The variability of imaging techniques used makes it impossible to compare results across studies. Indeed, counting metastases by less sensitive CT scan may lead to an underestimation compared to results of ^{18}F-FDG-PET/CT.

Standardizing imaging modalities is thus now a priority [22,34–36]. In their consensus document, ESTRO and ASTRO recommend the following: "PET/CT, contrast-enhanced chest/abdominal and pelvis computed tomography (CT) scans, and/or MRI brain or spine (when indicated) for diagnostic evaluation" [22]. The European Organization for Research and Treatment of Cancer (EORTC), along with ESTRO, propose a standardized imaging protocol as part of an OMD observational study implementation (Oligocare- NCT03818503) [36]. Recommendations for patients with OMBC to be included in Oligocare are presented in Table 2.

A synthesis of imaging issues in managing OMD has recently been presented by deSouza et al. [36]. Their study concludes that good assessment of the extent of metastatic disease requires sufficient sensitivity and specificity. Spatial resolution and tumor-to-background contrast values must therefore be optimized and validated. Since breast cancer tends to diffuse metastases to various organs (mainly brain, lung and liver, lymph node and bones), both organ-specific and a whole-body approach are called for. Imaging techniques currently being validated, such as Whole-body MRI (WB-MRI) or PET/MRI, have the advantage of combining morphological data with functional information. As optimal image contrast is determined by tumor biology, using specific radiotracers like 16α-[^{18}F]-Fluoro- 17β-estradiol (^{18}F-FES) can also optimize PET imaging.

Table 2
Current imaging guidelines and imaging recommendations for patients with OMBC to be included in Oligocare.

OMBC	
Recommendations for Oligocare inclusion	Conventional staging imaging per routine practice: -^{18}F-FDG-PET/CT at diagnosis - MRI Brain if above positive or in patients with neurological symptoms - If the primary clinical question is to detect or exclude liver metastases, MRI with liver-specific contrast agents designed to assess small lesions - Whole body-MRI if available, PET/MRI[a] if available

[a] Positron Emission Tomography/Magnetic Resonance Imaging with^{18} fluorodeoxyglucose.

Furthermore, it will be necessary to standardize the methods for acquiring and interpreting new imaging techniques. The METastasis Reporting and Data System for Prostate Cancer (MET-RADS-P), for example, may be a good model [37]. Finally, standardizing and validating more efficient imaging tools must be associated with implementing a protocol specifying their place in the different phases of OMBC management: screening, diagnosis, treatment evaluation, and follow-up.

deSouza et al. also raise the problem of follow-up after curative treatment of localized breast cancer. While prognostic factors are commonly used to predict metastatic relapse, no tools are available to predict oligometastatic diffusion [35]. To date, follow-up of patients treated curatively for localized breast cancer includes a clinical examination associated with an annual mammogram and ultrasound. No recommendation stands for other examinations such as tumor markers or other imaging tests. If, at some point, the benefits of a multidisciplinary strategy are proven, then diagnosing relapses earlier may also prove worthwhile [15,38]. Di Gioia et al. reported that enhanced monitoring, including tumor marker monitoring and ^{18}F-FDG-PET/CT, made it possible to diagnose limited-stage relapses, i.e., a maximum of three metastases confined to a single organ in 24.1% (7/29) of patients [39]. Jain et al., in another study of 114 patients with remote relapse, showed that OMBC incidence was 18.3% when the relapse was diagnosed according to symptoms and 42.1% when accidently discovered [40]. Studies on this question are underway [41].

In conclusion, imaging techniques for OMBC must meet the general criteria for OMD assessments. They must also take into account that breast cancer tends to diffuse metastases to numerous organs. Therefore, the most sensitive and specific imaging tools available to date should be used, both for exploring all organs of the body—^{18}F-FDG-PET/CT or WB-MRI— and where necessary for each organs frequently affected: brain, spinal and liver MRI. Nevertheless, it should be noted that WB-MRI could be considered, where available, recognizing that this is not possible in many countries. In our institution, we favor WB-MRI for low proliferative or lobular carcinoma and ^{18}F-FDG-PET/CT for other forms, liver MRI in case of suspected liver metastases, and brain MRI for all patients with HR-negative tumors, HER2-positive tumors or in cases of suspected brain metastases.

3.3. OMBC biology

The basic assumption about possible benefits of aggressive OMBC treatments is that they have a specific biology. We will see that even if knowledge of the physiopathology of metastatic diffusion has evolved over recent years, this has not been the case for that of OMBC biology.

3.3.1. Pathophysiology

Weichselbaum and Hellman have presented a theory reconciling the idea of orderly dissemination [42] and the concept of a potentially metastatic systemic disease at an early stage in its development [43,44]. According to these authors, breast cancers are distributed over a biological spectrum with the two extremes, from diagnosis, being diseases of local evolution and of systemic nature. OMBC would be an intermediate, biologically spatial and temporal stage between localized and polymetastatic breast cancer. In this case early treatment of primary and metastatic sites would be most appropriate for OMBC [9,10].

Knowledge acquired in the field of metastatic dissemination biology provides arguments in favor of this spectrum theory [45].

- The different steps towards metastatic spread are more clearly described: loss of cellular adhesion, increased motility and invasiveness, epithelial-mesenchymal transition, entry and survival in circulation, entry into new tissue, and colonization of a distant site [46–48].
- Metastatic dissemination is based on clonal expansion of cells that have acquired a part of the full metastatic potential [49].
- Evolution is not homogeneous, i.e., monoclonal, on all sites. There is significant genetic heterogeneity between the primary tumor and metastases [50,51].
- This heterogeneity is also found within the different sites, both primary and metastatic [52].
- Genomic alterations occur during the evolution of breast cancer and, as a result, the advanced breast cancer genomic landscape differs from that of early-stage breast cancer [53].

Thus, some breast cancers, from the beginning, would not be able to develop metastases, but would rather acquire this ability gradually [10]. The spectrum described by Weichselbaum and Hellman can therefore be compared to the progressive and heterogeneous acquisition of metastatic diffusion capacities, explaining the theoretical importance of treating the cancer before it develops its full metastatic diffusion amplitude.

3.3.2. Scarff-bloom-richardson's (SBR) grade, hormone receptor and HER2 status

Among studies presented in Table 1 and for which data are available [12,18], as well as in two observational series cited above [19,20], HR-negative tumors represent from 20 to 44% of all OMBC cases. HER2-positive represents 17–39% and SBR grade III tumors from 50 to 56%. Surrogate intrinsic subtypes, as defined by Harbert and al. [54], are described in three of these publications [12,17,19]. In these studies, triple negatives represent from 13 to 24%, and HER2-Enriched from 7 to 17% of OMBC. Aggressive breast cancer thus represents a non-negligible proportion of all OMBC. Finally, we found no publication showing a correlation between expression of HR, HER2 receptors, SBR grade of the primary tumor, or local relapse with the propensity of these cancers to evolve into an oligometastatic rather than a polymetastatic mode.

Moreover, van Ommen – Nijhof et al. evaluated OMBC prognostic factors for OS and/or PFS with multivariable analysis. Hormone-receptor positivity was associated with better outcome and HER2-positivity with worse. This latter result must be weighted, however, since few patients received anti-HER2 therapy [55].

3.3.3. CTCs

To date, CTC monitoring during metastatic breast cancer management provides prognostic information with no clinical implications [56–58]. As with other prognostic factors, it is not possible to affirm that it applies to the OMBC subgroup.

In managing OMBC, the value of CTC counts and their relation to the number of metastatic sites at diagnosis and during evolution have been explored by Giuliano et al. [59]. They conducted a retrospective analysis in a cohort of 517 patients to analyze the correlation between pre-treatment CTC level and initial spread of the disease. A first analysis focused on the correlation between the number of initial CTCs and the number of metastases present both at baseline and at progression. CTCs >5/7.5 ml before beginning systemic therapy significantly correlated with an increased baseline number of lesions and with organs involved. With progression, higher numbers of new sites and metastases were also significantly correlated. For patients with no visceral locations, CTCs >5/7.5 ml correlated with a shorter time before visceral metastases and overall survival (OS). Finally, for patients with a single metastasis, CTCs >5/7.5 ml were associated with a greater number of metastatic sites and lesions on progression and lower OS.

3.3.4. ctDNA

ctDNA is tumor-derived fragmented DNA released into the bloodstream. The search for genetic mutation in ctDNA makes it possible to overcome the problem of heterogeneity within a single tumor or between primary and metastatic lesions [60,61]. As with CTCs, determining ctDNA during metastatic breast cancer management provides information on prognosis [62–64], but this data is not applicable to OMBC due to the lack of dedicated studies [65].

3.3.5. miRNAs

miRNAs are RNA micro-molecules that control gene expression, among others, at the post-transcriptional level. They have been reported to be involved in all aspects of breast cancer pathophysiology, diagnosis and treatment [66,67]. miRNAs deregulation is associated with the different stages of breast cancer carcinogenesis up to the metastatic spread process. In addition, miRNAs provide important information for breast cancer diagnosis, progression, prognosis and follow-up treatment [68–71].

Non-breast cancer studies have shown the potential interest of miRNAs in characterizing oligometastatic cancers. Using a retrospective analysis of miRNA profile expression in 61 patients treated with Stereotactic Body Radiotherapy (SBRT) for metastatic disease in various types of oligometastatic cancers, a potential score has been identified to distinguish patients with better prognosis [72]. Another study including patients with less than five pulmonary metastases resected with curative intent demonstrated that miR-200c expression differentiated those patients who relapsed in a polymetastatic form from those in remission or with limited relapse [73].

3.3.6 Genomic characterization

Mutation profiles have been investigated for different types of oligometastatic cancers, but no publications have been found for OMBC [74]. Analysis of the whole genome has made it possible to describe a substantial majority of the somatic mutations in breast cancer. Almost all breast cancers have at least one driver mutation [50]. The number of somatic mutations varies widely among individual tumors [75].

Genomic alterations occur during the evolution of breast cancer and, as a result, the advanced breast cancer genomic landscape differs from that of early-stage breast cancer [49,52,76–78]. Advanced breast cancers have a higher mutation burden and clonal diversity than localized breast cancers. [53].

3.4. Arguments against the benefit of multidisciplinary treatment for OMBC

There are methodological and biological arguments against the

concept of OMBC and the possible benefit of aggressive treatments. Firstly, no study has formally demonstrated this benefit [79], and the retrospective analyses studied all have selection biases [80]. It would therefore be dangerous to implement aggressive strategies for patients with indolent and low-extension diseases for whom prolonged survival is not related to possible focal treatments, but rather to the nature of the disease itself. From a biological point of view, arguments in favor of an OMBC specific genotype are only theoretical, and there are no preclinical or clinical arguments supporting this hypothesis as compared to other types of cancer (i.e., pancreatic cancer [81] or kidney cancer [74]). Finally, it is possible that focal treatment of a primary tumor in patients with metastatic breast cancer may indeed have a negative impact, since the surgical removal itself of the primary tumor may release inhibitory molecules, growth factors and angiogenic factors [82]. Surgery and anesthesia may also increase immunosuppression [83].

3.5. OMBC incidence

Knowledge of OMBC incidence is thus crucial. If incidence is low, the public health issue will be moderate; if incidence is significant, proposing a curative treatment for OMBC becomes a strategic objective.

For several reasons, few data are available on OMBC, oligorecurrent or oligoprogressive breast cancer:

- The definition of OMBC is not standardized.
- The concept of a metastatic site is not clearly described.
- There is no standardization of medical imaging techniques.

According to many publications [16,18,36,39,82,84–87] OMBC accounts for less than 10% of newly diagnosed cases of metastatic breast cancer. But these publications all refer, directly or not, to a single article [88]. In this study, no patient benefitted from CT scans, MRI or ^{18}F-FDG-PET/CT as part of their staging investigation. Moreover, these were only oligorecurrent diseases.

One publication reviewing six randomized trials of first-line metastatic chemotherapy or hormone therapy in 2522 patients showed that the number of patients with fewer than two metastatic sites varied from 49% to 57%. These patients were described as oligometastatic. But for these authors, the term “site” clearly corresponded to an affected organ, and not to a single metastatic lesion [32].

Four publications provide first-hand data on OMBC incidence. The first concerns a retrospective series of 767 patients consecutively treated in a single institution for *de novo* or recurrent stage IV breast cancer from 2014 to 2018. In this series, patients were considered to have OMBC if at diagnosis they presented one to five disease sites including the primary tumor, regardless of whether focal treatment was feasible. Among them, 131 had *de novo* OMBC or oligorecurrent breast cancer. This corresponds to an incidence of 17.1% [19].

Two publications provide data on oligorecurrent breast cancer. In these studies, this form of breast cancer is defined as initially localized and later relapsing with five metastases or less. A retrospective series including 1869 patients treated in two institutions for stage I to III localized breast cancers showed that 111 of these patients had a distant relapse. Among the latter, 77 met inclusion criteria (follow-up >3 years after metastatic relapse or until death or progression with more than five metastases). Among these 77, 13 (16.9%) had less than five metastases at relapse [89]. In a second retrospective analysis of a cohort of 2249 patients treated for localized breast cancers, 114 patients had a distant relapse, and 25 (21.9%) had less than five metastases [40].

Kelly et al. analyzed a series of 512 patients treated consecutively for hormone positive receptor metastatic breast cancer. One hundred and eight patients experienced at least one episode of disease progression. Among these patients, 11 were oligometastatic (<6 sites) at diagnosis and 97 were initially polymetastatic. Thirty-one percent (34/108) of the patients experienced at least one oligoprogression, i.e. progression while under hormonal treatment in fewer than three sites [33].

3.6. OMBC therapeutic strategies

What objective for treatment, we may then ask, should be set in the context of a disease where remissions can be long and relapses late: absence of relapse, prolongation of OS equal to that of healthy women of the same age or maintenance of an indolent, asymptomatic, controlled disease through well-tolerated medical treatment [38,82]? We believe that the question is worth asking. In any case, other end points must be considered like quality of life, toxicity, cost, or the possibility of maintaining the same systemic therapy [22].

To date, only ASTRO-ESTRO and ESO-ESMO recommend a curative treatment strategy, when possible, for OMBC. The American Society of Clinical Oncology (ASCO) has made recommendations, but limited to patients with one to four encephalic metastases of HER2-positive breast cancers [90].

If the benefits of aggressive strategy have not yet been clearly demonstrated, many reviews seem to confirm the feasibility and relative safety of focal treatments using surgery, SBRT or percutaneous image-guided treatment. SBRT is increasingly used in treating bone and visceral metastatic sites [91]. Tree et al. published a review of 28 trials using SBRT for metastatic sites of OMD of any histology [92]. The local control rate was around 80% and grade III acute and late toxicity less than 9% in all studies but one. The authors concluded that “SBRT for oligometastases is safe and effective”.

In hepatic surgery for OMBC, one meta-analysis has reported median mortality and complication rates of, respectively, 0% and 21% with a 40% median five-year survival rate [93]. In a second meta-analysis of post breast cancer liver metastasectomy, median mortality varied from 0% to 5.9%, with a median morbidity rate of 15%. [94]. The authors noted that these procedures resulted in few serious complications, considering that were performed in expert centers. A third meta-analysis found that 30-day morbidity and mortality rates were, respectively, 20% and 0.7%; median OS was 36 months (12–58 months) [95]. In a meta-analysis concerning breast cancer lung resection, five-year survival rate after pulmonary metastasectomy was 46%. The authors remind us that lung metastasectomy is associated with low perioperative morbidity and mortality [96,97]. Unfortunately, none of these meta-analyses of breast cancer liver and lung metastasectomy provide data on local control.

Considering image-guided metastatic ablation, a retrospective review of 566 patients treated with radiofrequency for metastases of various primitive origins has confirmed the low level of mortality/morbidity [98]. Another retrospective analysis of 79 patients treated with percutaneous thermal ablation for 114 breast cancer metastases in various locations reported local control rates, respectively, of 83.0 and 76.1%. There was no mortality and 15% morbidity (no grade of toxicity was described) [99].

4. Discussion

If we consider that breast cancer is represented by a continuous phenotypic and genotypic spectrum, where OMBC lies between localized and polymetastatic breast cancer, the idea of

implementing a curative strategy for complete remission including both systemic and focal treatments at all metastatic sites is based on two observations.

First, in managing localized or micrometastatic breast cancer, complete histological remission by neoadjuvant chemotherapy is a favorable prognostic factor for certain molecular subtypes [100,101]. Furthermore, stage IV breast cancer with no evidence of clinically measurable disease (Stage IV-NED) following local or systemic treatment also has a favorable outcome [7,8,102]. However, it remains unclear whether remission by focal treatment is equivalent to chemotherapy-induced remission. To answer this question, randomized controlled trials must be set up. If this is not possible, clinical studies with a lower level of evidence, but with homogeneous populations and sufficient numbers of patients, must be carried out. This first requires a consensual definition of OMBC and standardized imaging protocols for initial assessment and follow-up.

To date, the only proposed definitions of OMD and OMBC have been provided by ESTRO-ASTRO [22] and ESO-ESMO [21]. These definitions include a maximum cut-off of five metastases and no limited number of organs involved. Although both these definitions include the notion of a maximum number of metastases, ESTRO-ASTRO further specified that, in clinical practice, "the feasibility of safely delivering curative intent MDRT [metastasis-directed radiotherapy] determines the maximum number of lesions and sites that can be treated with radiotherapy in OMD" [22].

The choice of five metastases as a threshold seems relevant when considering studies describing the distribution of patients according to the number of metastases present. However, ESTRO-ASTRO [22] and ESO-ESMO [21] introduce in the definition of OMBC the feasibility of focal treatment of metastatic sites. This leads to a certain subjectivity since feasibility depends on the technical capabilities of each team. In our opinion, this consideration should not be part of the definition of OMBC, but rather be discussed in relation to inclusion criteria of interventional studies. Additionally, the term "metastatic site" should be avoided, given the possible confusion between the number of metastases and the number of organs invaded. Kelly et al. have proposed a pertinent definition of the metastatic lesion [33]. While certain points still deserve further specification, this position at least offers a functional starting point. Standardizing imaging techniques, according to what ASTRO, ESTRO and EORCT [22,36] recommend, would also be a positive step towards consistently counting the number of metastases as new techniques emerge. Finally, methods of acquisition, interpretation, and reporting must be standardized.

Few data are currently available concerning OMBC biology. The expression of HR and HER2 receptors and the value of SBR grade of the primary tumor or its local recurrence do not predict a possible evolution towards an oligo- or a polymetastatic stage. Nor do they make it possible to predict potential benefits of treatments with a curative intent.

In various contexts, miRNA and specific somatic mutation profiles seem to provide information about the benefits of multidisciplinary treatments for OMD [71–73]; these profiles should thus be tested on OMBC.

In the end, a single study exists in OMBC biology linking a biological parameter — CTC count — to the oligometastatic evolution of breast cancers [59]. Nevertheless, it provides no knowledge of the biological mechanisms involved, reflecting only the correlation between quantitative data and progression modes of breast cancer. More biological studies must therefore be implemented exploring this essential subject, being initially based on an eventual specific biology [9]. Moreover, if OMBC has specific biological mechanisms, more fully understanding them would significantly contribute to better understanding the biology of breast cancer metastatic spread in general.

As for OMBC epidemiology, the literature is limited. A single publication provides data on OMBC incidence in a series of 767 MBC: 17.1% [19]. Another study is obsolete [88] due to outdated imaging. Two studies provide data on oligorecurrent breast cancer, respectively, 16.9 and 21.9% [40,89]. A fifth provides an oligoprogressive hormone positive receptor breast cancer incidence of 31% [33]. Observational studies will make it possible to further specify/clarify this data.

OMBC prognostic factors cannot be deduced from those of polymetastatic breast cancers. In a systematic review, five prognostic factors of OMBC (either favorable or unfavorable) have been identified. These include: a single metastasis, >24 months interval between primary tumor and OMBC, no or limited involvement of axillary lymph nodes at primary diagnosis and hormone-receptor positivity appear to be favorable prognostic factors. HER2-positivity seems to be an unfavorable prognostic factor, but most patients included in the studies did not receive anti-HER2 treatments [55].

As for therapeutic strategies, no studies to date prove with a sufficient level of evidence the benefits of an aggressive strategy combining ablative treatment of all affected sites and systemic therapy in terms of progression-free or OS in OMBC. Surgery, radiotherapy, and percutaneous image-guided treatment do, however, appear to make it possible to treat metastatic sites with a low rate of complications and a high rate of local control. The low morbidity and mortality rates of these treatments must be taken into account when deciding whether to treat metastatic sites of OMBC.

Three on-going randomized studies are evaluating the benefit of treating OMBC metastases [103–105]. For many reasons, implementation of randomized controlled trials in OMBC multidisciplinary treatment is difficult. First, these potential studies compete with trials of new drugs in first-line treatment. Second, the ethical question of proposing therapeutic abstention for metastatic sites cannot be ignored since several learned societies recommend such aggressive strategy. Recent progress achieved in metastatic breast cancer treatment, in particular the use of cyclin-dependent kinase inhibitors, mTOR and PI3K inhibitors, new anti-HER2 molecules, immune check point inhibitors and antibody-drug conjugates, however, may render the results of these randomized studies obsolete as soon as they are published. Finally, OMBC appears as a heterogeneous entity, due to the variety of organs involved and the diversity of the surrogate intrinsic subtypes of the tumors. It may then be necessary to evaluate such intention-to-cure treatments for each of these sub-groups.

In conclusion, establishing prospective observational cohort studies in parallel to medical therapeutic trials would be a sound alternative. These observatories could be associated with ancillary studies for biological analysis, quality of life, and medico-economic evaluation. In the absence of formal proof of the benefit of multidisciplinary treatments of OMBC, such an approach would at least increase our knowledge of the efficacy and safety of focal interventions, OMBC epidemiology, and biology, as well as the impact of treatments on quality of life.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

We would like to thank Dr. Gail Taillefer, native speaker experienced in scientific publication and Emeritus professor of English, for her review of the manuscript.

Our thanks also to Jean Christophe Babinet, Rachel and Stephanie for their re-readings and ever-relevant reflections.

And thanks to Stephanie, Rachel, Barbara and Simon for their presence at all times.

Appendix 1. Search strategy

Diagnosis, biology and epidemiology of oligometastatic breast cancer.

Jean-Louis Lacaze, Richard Aziza, Ciprian Chira, Eleonora De Maio et al.

We have searched the PubMed database. Algorithms are presented here for each key word. For two searches, PubMed filters were used and are detailed below.

Number of articles by theme1

Themes	Review	Biology	Imaging	Clinical studies	Total	Without duplicate
Number of articles	70	5	11	51	137	96

2 ALGORITHMS

2.1 Algorithm # (OMBC) =*

- ("oligometas*"[Title/Abstract] OR "oligo metas*"[Title/Abstract] OR "solitary metas*"[Title/Abstract] OR "isolated metas*"[Title/Abstract] OR "single site metas*"[Title/Abstract] OR "limited disease"[Title/Abstract] OR "limited volume"[Title/Abstract] OR "limited recur*"[Title/Abstract] OR "solitary recurr*"[Title/Abstract] OR "rate of recurr*"[Title/Abstract] OR "pattern of recurr*"[Title/Abstract] OR "isolated recurr*"[Title/Abstract] OR "metastatic dissemination"[Title/Abstract]) AND ("breast cancer"[Title])

  *OMBC: oligometastatic breast cancer

*2.2 Algorithm #(OMD)** =*

- ("oligometas*"[Title/Abstract] OR "oligo metas*"[Title/Abstract] OR "solitary metas*"[Title/Abstract] OR "isolated metas*"[Title/Abstract] OR "single site metas*"[Title/Abstract] OR "limited disease"[Title/Abstract] OR "limited volume"[Title/Abstract] OR "limited recur*"[Title/Abstract] OR "solitary recurr*"[Title/Abstract] OR "rate of recurr*"[Title/Abstract] OR "pattern of recurr*"[Title/Abstract] OR "isolated recurr*"[Title/Abstract] OR "metastatic dissemination"[Title/Abstract])

  **OMD: oligometastatic disease

2.3 Algorithm #(IMAGING) =

- ("imaging"[Title/Abstract] OR "MRI"[Title/Abstract] OR "CT"[Title/Abstract] OR "PET"[Title/Abstract])

2.4 Algorithm #(REVIEW)

- ("Review*"[Title/Abstract] OR "meta-analysis"[Title/Abstract] OR "Guideline*"[Title/Abstract])

2.5 Algorithm #(STUDIES)

- ("clinical trial"[Title/Abstract] OR "phase II"[Title/Abstract] OR "phase III"[Title/Abstract] OR "clinical study"[Title/Abstract] OR "comparative study"[Title/Abstract] OR "retrospecti*"[Title/Abstract] OR "Prospecti*"[title/Abstract] OR "observation*"[title/Abstract])

3 REVIEW

We used two methods, one using PubMed Filters, one with an algorithm #(REVIEW)

3.1 With PubMed filters

- # (OMBC) and PubMed filters: review, systematic review, meta-analysis, guidelines

  91 results; 31 articles selected.

3.2 With #(REVIEW) algorithm

- #(OMBC) AND #(REVIEW)

  110 results; 39 articles selected.

4 BIOLOGY

4.1 miRNA

- #(OMBC) AND ("Circulating MicroRNA"[Title/Abstract] OR "Cell-Free MicroRNA"[Title/Abstract] OR "Cell Free MicroRNA"[Title/Abstract] OR "MicroRNA"[Title/Abstract])

  8 results; 4 selected.

4.2 ctDNA

- # (OMBC) AND ("ctDNA"[Title/Abstract] OR "Circulating Tumor DNA"[Title/Abstract] OR "Cell-Free Tumor DNA"[Title/Abstract])

  Results, no articles selected.

4.3 CTC

- #(OMBC) AND ("CTC"[Title/Abstract] OR"CTCs"[Title/Abstract] OR "Circulating tumor cell*"[Title/Abstract])

  12 results, 11 not related to OMBC, 1 selected.

4.4 GENE

- #(OMBC) AND ("gene*"[Title] OR "Mutati*"[Title] OR "profil*"[Title] OR "DNA"[Title] OR "sequenc*"[Title] OR "expression pattern"[Title] OR "array"[Title] OR "transcript*"[Title] OR "epigenet*"[Title] OR "genetic"[Title] OR "genomic"[Title] OR "gene expression"[Title] OR "chromosome*"[Title])

14 results, no article selected.

5 IMAGING TECHNIQUES

The research was widened to OMD.

We used two methods, one using PubMed filters, one with an algorithm #(REVIEW)

5.1 with PubMed filters

- # (OMD) AND # (IMAGING) and PubMed filters:

review, systematic review, meta-analysis, guidelines.

55 results 6 articles selected.

5.2 With #(IMAGING) and #(REVIEW) algorithm

- # (OMD) AND # (IMAGING) AND #(REVIEW)

415 results 5 articles selected.

6 CLINIAL STUDIES

We used two methods, one using PubMed filters, one with an algorithm #(REVIEW)

6.1 With PubMed Filters

- # (OMBC) and PubMed filters:

Clinical Study, Clinical Trial, Comparative Study, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Randomized Controlled Trial, Systematic Review.

46 results; 15 articles selected.

6.2 With #(STUDIES) algorithm

#(OMBC) AND ("clinical trial"[Title/Abstract] OR "phase II"[Title/Abstract] OR "phase III"[Title/Abstract] OR "clinical study"[Title/Abstract] OR "comparative study"[Title/Abstract] OR "retrospecti*"[Title/Abstract] OR "Prospecti*"[title/Abstract] OR "observation*"[title/Abstract])

111 results: 26 articles selected.

After removing duplicates, 43.

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