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REVIEW ARTICLE

Oligometastatic breast cancer

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Abstract
Metastatic breast cancer (MBC) is considered as incurable. The group of patients with oligometastatic disease (a few metastatic lesions and organs involved) apparently have better prognosis. It is claimed that, these patients could be treated with curative intent, and multidisciplinary aggressive approach should be considered. Despite the lack of strong data it is increasingly accepted in clinical practice. Currently, the appropriate candidate would be young woman with good performance status, low tumour burden with long disease-free interval. Because for them with already favorable nature of their disease, aggressive treatment has greater chances to improve survivals. Local ablative treatment (radiotherapy/surgery) has a crucial role in this setting. Available mainly from retrospective in nature long-term results are encouraging but need confirmation in prospective randomized studies. In this review, I discuss the definition of oligometastatic disease, its nature, currently available data and ongoing prospective randomized trials dedicated to oligometastatic breast cancer patients.

Keywords Oligometastatic · Breast cancer · Surgery · Radiotherapy

Introduction

Metastatic breast cancer (MBC) is an incurable disease. Systemic therapy is the standard of care for this group of patients [1]. The development of new drugs have led to improved overall survival (OS) of patients with MBC. Stage IV at diagnosis constitutes 3.5–7% of all new breast cancers (BC). Among the entire population suffering from BC almost 30–40% will develop widespread metastases [2–4]. Then, median OS ranges between 8 months and 4 years [5–8]. Several factors have influence on the survival and some of them are cancer-related as follows: tumour biology, tumour burden and type of involved organ. Patients with visceral metastases have unfavorable prognosis especially compared to those with bone-only metastases [9].

However, in clinical practice we can find long-term survivors. Some patients (1–3%) who achieve a complete response (CR) remain free of disease even beyond 20 years [10, 11]. They are usually young, have good performance status and limited metastatic disease [5, 6].

The theory that many cancers have at the beginning only few metastases without widespread potential was created [12, 13]. This group of patients with oligometastatic disease (OMD) is considered as "potentially curable" [5]. This "intermediate stage" is estimated to be 1–10% of newly diagnosed MBC [5, 14]. Nowadays, along with developing diagnostic tools OMD can be diagnosed more often. Theoretically, systemic treatment and local therapy (forced CR) in this group can improve outcomes.

The European School of Oncology–Metastatic Breast Cancer (ESO–MBC) Task Force pointed that: "A small but very important subset of MBC patients, for example, those with a solitary metastatic lesion, can achieve complete remission and a long survival. More aggressive and multidisciplinary approach should be considered for these selected patients. A clinical trial addressing this specific situation is needed" [15].

In this review, I discuss the nature of oligometastatic disease, currently available data and ongoing prospective randomized trials dedicated to oligometastatic breast cancer patients (OMBC).

Theories of metastasis

The metastatic disease is very diverse with a variable clinical course. In clinical practice, we can find patients who developed metastases in a short period of time or many years after

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treatment of primary tumour. Independently, they can have low tumour burden metastatic disease or its massive manifestation. It is related with different prognosis and the worst is for rapid reccurrence with high tumour burden. Definitely, on the basis of these various clinical forms lie different biological processes.

In 1894, Halstead proposed the theory that cancer was a disease that direct spread from primary tumour to regional lymph nodes and then to distant sites [16, 17]. Later, the 'systemic theory' of metastasis suggested that widespread dissemination is from the beginning and tumour is only a manifestation of already existing systemic disease [2, 18, 19]. These two opposite hypotheses do not fulfill the clinical observations. In 1995, Hellman and Weichselbaum described an idea of an oligometastatic disease as an intermediate state (limited in number metastases and involved organs) in the spectrum of metastatic disease [12, 13, 20–22]. It is suggested that oligometastatic tumours may not have enough genetic changes to rapidly develop widespread metastases and their potential is limited to the involvement of one or two organs. On the other hand, there is a theory of chromothripsis which explains the development of "massive widespread metastases by massive de novo structural rearrangement formation in a one-step catastrophic genomic event" [23, 24].

The definition of oligometastatic disease

The 'oligo' word has its origin from Greek ('oligos') and is a prefix denoting few or little [25]. The exact number of metastatic lesions and involved organs as a definition of OMD vary in the literature but usually do not exceed 5 and 2, respectively. Unfortunately, the definition is not unified what makes comparison of the results even more difficult. For instance, according to the ABC3 (The Advanced Breast Cancer Third International Consensus Conference) vote there should be a maximum of 5 lesions, which do not necessarily have to be in the same organ [16]. For German experts OMD is defined as a limited number of metastases in one organ [16]. Generally, there should be a few lesions with limited number of region involved with major difference in control of primary lesion between oligometastases and oligo-recurrences which is required in the oligo-recurrence (recurrent or metastatic sites should be potentially amenable for local treatment) [20]. It is important to distinguish these cohorts because probably they have different prognoses.

Currently, definition does not take into account disease-free interval (DFI). Although, it seems that patients who developed few metastatic lesions in one organ, e.g. in 3 months or years after radical treatment have different prognoses. Results from several studies indicate that natural course of disease prefers OMD patients as a potential long-term survivors [22, 26–28].

Local treatment

Surgery

Incidence-adjusted metastasectomies for BC increased from 2000 to 2011 in the United States with the brain metastasectomy as the most commonly performed procedure [29]. Liver metastasectomies showed the highest rate of increase of any metastatic site [29].

The lung and liver resections are one of the most frequently reported surgical treatment for BC. The median survival after removal of pulmonary metastases ranged from 32 to 97 months with 5-year OS rate from 27 to 80% [30, 31]. Regarding lung metastasectomy, the most valuable data comes from the International Registry of Lung Metastases [30]. In this retrospective study, patients with simultaneous resections of the primary tumour and metastases in other organs were also included [30]. Approximately, 66% and 10% of the patients had a single and more than three pulmonary metastases, respectively. In 467 BC patients complete resection (R0) was possible in 84%. Median OS and 5-year OS rate were 37 months and 38% in group with R0 and 25 months and 18% in group with incomplete resections, respectively [30]. For all cohort the median OS, 5-year and 10-year survival rate were 35 months, 35% and 20%, respectively [30]. In the group with R0, the significant prognostic factor was DFI > 36 months. In other studies, it varies between 12 and 48 months [32–34]. Solitary metastasis was associated with non significant better survivals [30].

In the small study, OMD defined as less than 5 lesions restricted only to lung was a significant prognostic factor for long-term survival after metastasectomy [35].

The median survival after hepatic resection for BC metastases ranged from 14.5 to 63 months with 5-year OS rate from 14 to 61% [5]. In 2004 and in 2012 experiences of The University of Texas MD Anderson Cancer Center regarding resection of liver metastases from BC has been published [36, 37]. The majority from 86 highly selected patients who underwent resection had solitary metastasis. Patients with controlled extrahepatic disease were included. In 90% R0 resection was performed without significant influence on OS. The median OS and 5-year OS rate were 57 months and 43.6%, respectively [37]. Those with ER/PgR (progesterone receptor)–positive tumours had improved OS. Moreover, those who had at least partial response (PR) to chemotherapy before resection and those without response had median OS approximately 80 months and 30 months, respectively [37].

Radiotherapy

Stereotactic body radiation therapy (SBRT) is an external beam radiotherapy used to very precisely deliver a high dose of radiation to an extracranial target within the body [38]. The dose is deposited using either one or a few fractions with maximum sparing of normal tissue [38]. The biological advantages of high-dose radiotherapy are "the greater potential cell kill and a potential reduction of the deleterious effect of tumour proliferation" [39].

Choosing the correct dose, we have to take into account type of organ with the metastasis, surrounding healthy tissues (organs at risk) and expected effect on the target. Approximately, 1 logarithm cells in radiosensitive tumours should be killed by dose of 7 Gy [40]. It is claimed that ablative radiotherapy dose is when biologically effective dose (BED) is larger than 100 Gy [41, 42]. There are some premises that BED of 75 Gy might be enough to eradicate viable tumour cells [42, 43].

Treatment dose

Salama et al. created the dose escalation trial to find the appropriate dose [44]. In 2012, they presented final report of this study with median follow-up of 20.9 months [45]. Patients with stage IV cancer who had no more than 5 malignant sites were eligible for this prospective trial [45]. Brain metastases were required to be treated and controlled before enrollment [45]. Most of the patients had 1 metastatic site. Sixty-one enrolled patients had tumours of diverse primary origins, including BC ($n=7$) [45]. The starting total dose was 24 Gy to maximum total dose of 48 Gy delivered in 3 fractions [45]. The worst lesion control was observed after delivered 24 Gy [45]. Results from this study, in concordance with others, suggest increasing metastasis control with higher radiation doses [45–47]. Patients with 1–3 and 4–5 metastases developed widespread metastatic progression in 46% and 75%, respectively [45]. Two-year PFS and OS are 22% and 56.7%, respectively [45]. Considering these results, we have to be aware that 80.3% of patients received systemic treatment before enrollment [45].

Wong et al. tried to characterize clinical and molecular markers of long-term survival after oligometastasis-directed SBRT in group of patients indicated above [41]. Researchers observed no statistically significant impact on treated metastasis control (TMC) for any type of cancer, including BC [41]. Patients who had BC had a median, 2-year, and 5-year PFS of 2 years, 57%, and 29%, respectively, and results were non significantly better than for patients who had nonbreast cancer [41]. For this group of patients, the median, 2-year, and 5-year OS estimates were significantly better than for patients with nonbreast cancer and were 4.3 years, 100% and 50%, respectively [41]. BC histology was significantly associated with a decreased risk of death [41]. In cohort who received a minimum dose of 36 Gy to all treated metastases outcomes were better in terms of TMC, PFS, and OS [41]. The information regarding molecular markers in BC patients are limited because only one sample available for micoRNA testing was from this tumour [41]. The progression was observed mainly beyond the irradiated lesions. More than half of all patients had distant metastasis-free interval of less than 12 months. Moreover, more than half of all included patients progressed during 6 months after completion of SBRT [41].

In total, 309 patients (11% BC) with no more than 5 metastases at any site were included in the retrospective analysis [42]. The median delivered BED_{10} was 60 Gy [42]. More than 70% of patients had only one metastatic site involved [42]. In 46.3% cases only one metastasis was detected [42]. Nonadenocarcinoma histology, intracranial oligometastatic disease, latency time of <12 months, extranodal metastatic disease, synchronous occurrence of oligometastases, male gender and dose $BED_{10}<75$ Gy were associated with significantly impaired OS [42]. $BED_{10}\geq 75$Gy was correlated with a statistically significant superior OS and local control (LC) [42]. Number of metastases had influence on OS in cohort with extracranial sites [42]. Median and 5-year OS rates were 24 months and 19%, respectively [42]. Recently, it was confirmed that higher BED is associated with OS [48].

Studies with mixed cohorts

Milano et al. separately evaluated results for 39 BC patients [49]. One hundred twenty-one patients with ≤ 5 metastases were enrolled in prospective studies with curative-intent SBRT. The preferred total dose was 50 Gy in 5 Gy fractions [49]. One patient had brain-only disease and nine patients had bone-only disease. Eight of them had BC [49]. Approximately, 80% of patients had only one organ and a maximum of 3 lesions involved [49]. The median survival and PFS were 24 and 11 months, respectively. The 4-year OS, PFS and LC rates were 28%, 20% and 60% respectively (Table 1) [49]. Patients with BC were long-term survivors (≥ 2 years) [49]. Neither the number of organs involved nor the number of oligometastatic lesions were significant for the outcomes [49]. Patients with primary BC had significantly improved OS, PFS, LC compared to patients who had nonbreast cancer [49].

A few years later Milano et al. have published updated results with median follow-up for BC patients of 4.5 years [50]. Women with BC were significantly younger, more likely to be treated for bone metastases and to have received systemic therapy for metastatic disease. Below are indicated only results calculated for BC patients. One-third of them

Table 1 Radiotherapy in oligometastatic breast cancer patients

Study [References]	No. of pts with BC	Max. No. of metastatic lesions/organs (max. lesion diameter)	Systemic treatment for OMD prior to enrollment	Treatment	LC	PFS	OS
Wong et al. [41]	7	5/NA (≤10 cm/≤500 mL)	NA	SBRT 24Gy–48Gy	NA	Median—2 years 2-year—57% 5-year—29%	Median—4.3 years 2-year—100% 5-year—50%
Milano et al. [50]	39	5/3	Yes B and/or A	SBRT 5 Gy/fr. (50 Gy)	2-year—87% 4-year—87% 6-year—87%	FFDM 2-year—52% 4-year—43% 6-year—36%	2-year—74% 4-year—54% 6-year—47%
Lee et al. [51]	50	NA	NA	SBRT 5 Gy/fr. (50 Gy)[a]	2-year[b]—78%	NA	2-year—81%
Milano et al. [52]	40	5/3	Yes B/A	SBRT	Patient LC 2-year—80% 4-year—80% tumor LC 4-year—89%	Median—23 months 2-year—44% 4-year—38%	2-year—76% 4-year—59%
Kobayashi et al. [53]	75	5 per organ [10 in lungs or bones]/2 (≤5 cm)	Yes B/A	CT→ (CR/PR) Surgery or RT → CT	mRFI—48 months RFR 5-year—45% 10-year—27.4% 15-year—27.4% 20-year—27.4%	Median—68.5 months 5-year—56.8% 10-year—32.8% 15-year—29.1% 20-year—29.1%	Median—185 months 5-year—79.2% 10-year—59.2% 15-year—51.2% 20-year—34.1%
Yoo et al. [54]	50	5/NA	Yes	RT 20–60Gy (median 30 Gy)	3-year—69.6% 5-year—66.1%	NA	2-year—85.2% 5-year—49%
Scorsetti et al. [55]	33	4/2 [liver or lung][c] (<5 cm)	Yes B/A	SBRT 48Gy–75Gy in 3–4 fractions	1-year—98% 2-year—90%	Median—11 months 1-year—48% 2-year—27%	Median—48 months 1-year—93% 2-year—66%

pts patients, *OMD* oligometastatic disease, *LC* local control, *PFS* progression-free survival, *OS* overall survival, *NA* not applicable, *SBRT* stereotactic body radiotherapy, *B/A* before and after, *fr*. fraction, *FFDM* freedom from widespread distant metastasis, *CT* chemotherapy, *RT* radiotherapy, *CR* complete response, *PR* partial response, *mRFI* median relapse-free interval, *RFR* the relapse-free rate

[a]Some of patients were treated on a three fraction dose escalation study

[b]TMC, treated metastasis control

[c]Other metastatic sites stable or responding after chemotherapy were allowed

were alive at the last follow-up visit (>4 to 10 years) without widespread metastatic disease [50]. The 2-

and 6-year OS rates were 74% and 47%, respectively (Table 1) [50]. Usually, there is uncertainty if in BC group tumour biology, patient selection, systemic treatment or ablative local treatment has the strongest influence on better outcomes in case of OMD. In this study, patients with progression of the disease before SBRT was initiated had significantly worse 2-year OS rate compared to those who had at least stable disease (55% vs 81%) [50]. Fifty-seven percent long-term BC survivors had one initial metastatic lesion [50]. Patients who died 4 years after SBRT had not developed local failure. Two long-term BC survivors had local failure which was treated locally with a good result [50].

In the Lee at al. study patients with MBC had significantly better 2-year OS and TMC rate than other histologies. In the all cohort (predominant lung cancer, BC, colorectal cancer) patients with one treated metastasis and bone-localisation had significantly better 2-year OS rates [51]. Recently, Hong et al. identified patients with breast, prostate, or kidney cancers or long DFIs, who are most likely to benefit from aggressive local treatment [48].

Studies with breast cancer patients only

Milano et al. designed prospective pilot study to assess patient outcome after SBRT for limited BC metastases (ER/PgR-positive of 63%) [52]. Systemic therapy was administered prior and after SBRT in 36 and 32 cases, respectively [52]. Six patients received local therapy for OMD before enrollment [52]. The most common site of metastasis was liver followed by lung, bones, thoracic lymph nodes and pelvic or abdominal lymph nodes [52]. The 2-, 4-year OS were 76%, 59%, respectively (Table 1) [52]. Using univariate analysis, there was significant difference between patients with 1 lesion vs > 1 lesion, what was not confirmed on multivariate analysis [52]. Patients with bone-only disease had better outcomes [52].

Kobayashi et al. have published data from retrospective analysis conducted in OMBC patients treated within 30 years in one institution (Table 1) [53]. There was a preponderance of patients with positive status of hormone receptors (HR), human epidermal growth factor receptor 2 (HER2)–negative and low Ki67 level defined as < 14%. Most patients had only one involved organ. Chemotherapy as an initial treatment for OMBC received of 88% patients, followed by local treatment. Those who achieved CR or PR received additional systemic treatment [53]. Significantly higher CR or CR/no evidence of clinical disease (NED) rates had those with only one organ involved with metastatic lesions, whose received multidisciplinary treatment and anthracycline-based regimens for OMBC. The estimated median OS was 185 months [53]. Significant influence on OS had: single involved organ (mOS of 292 months), local therapies, absence of liver metastases, and anthracycline-based chemotherapy [53]. The OS was also significantly longer in patients with CR/NED (estimated mOS 192.2 months). The selected outcomes are listed in Table 1.

In Yoo and colleagues` series patients with extracranial oligometastases from BC were analysed [54]. Because of metastatic disease 2 patients have undergone surgery, 12 received chemotherapy, 34 endocrine therapy and 20 were treated with bisphosphonate [54]. All patients had bone metastases and for 43 of them that was the only localisation of metastases [54]. The 2-year OS rate for all patients and for solitary bone metastasis group were 85.2% and 96.7%, respectively (Table 1) [54]. HER2–negative status and BED ≥ 50 Gy were significantly associated with improved LC by univariate analysis. Higher dose was favorable prognostic factor with marginal significance for the LC [54]. The higher dose had an impact on the irradiated lesion control but not obvious influence on OS. The presence of HR and solitary bone metastasis were independent favorable prognostic factors for the survival [54]. In this retrospective study, patients mainly received BED < 50 Gy and still had OS comparable with other studies and even better LC. This partially might be explained because most patients had bone-only metastasis which is known to be a factor associated with improved survival compared to visceral metastasis [9, 54]. These findings support the results from Milano et al. study [52]. Authors indicated that the most favorable group would be patients with solitary bone metastasis who received high-dose radiotherapy on entire defined target as soon as possible [54].

Patients with metastases in the lung or liver were treated by Scorsetti et al. [55]. Other metastatic sites stable or responding after chemotherapy were allowed and were not the objects for SBRT. More than 90% of patients received systemic therapies for metastatic disease before and all of them after SBRT [55]. Usually, the applied dose was higher than in previous studies and for liver and lung lesions was 56.25–75 Gy in 3 fractions and 48 Gy in 4 fractions, respectively [55]. Only two patients developed progression of the disease in the treated target [55]. In this study, the local disease control was excellent even when the main group was with less favorable visceral lesions. This can be partially explained by the higher deposited dose to the target [55]. However, the survival outcomes were worse as compared to Milano et al. study [52, 55].

Other local treatments

The French investigators retrospectively evaluated the effectiveness of percutaneous thermal ablation in more than 70 patients with oligometastatic/oligo-recurrence BC [56]. The most commonly treated metastatic site was liver (63%) followed by bones and lung. Almost all patients had only one organ involved. All patients received systemic treatment before and after local therapy. The 2-year OS and LC were 95.5% and 76.1%, respectively [56]. Tumour burden was associated with a poorer outcome for LC and disease-free-survival (DFS). “Triple-negative” metastases had influence on poorer DFS [56].

Ongoing studies

In the ongoing phase III randomized STEREO-SEIN trial investigators want to evaluate the role of SBRT in de novo OMD and compare this approach to systemic treatment alone. This study is dedicated to patients with HR–positive MBC with no more than 5 metastatic lesions. The primary outcome measure is PFS evaluated with a minimal follow-up of 3 years in all patients [57]. The similar design studies NCT02364557, NCT02759783, and NCT01446744 are ongoing [57, 58]. The results from these studies probably will answer the question whether standard of care therapy with local treatment (SABR/surgery) is more effective as compared to standard of care therapy alone. Researchers

at the MD Anderson Cancer Center also want to check if combined treatment mentioned above can help to control the disease for a longer period of time in limited bone-only MBC (NCT00929214) [57].

In another phase III clinical trial investigators want to compare the effect of high-dose alkylating chemotherapy to standard chemotherapy as part of a multimodality treatment approach in patients with OMBC harboring homologous recombination deficiency [57]. The currently ongoing clinical trials in OMBC patients are listed in Table 2.

Table 2 Ongoing studies in OMBC (August 2018) [57]

Study number (Study name) [References]	Phase	Primary tumor site controlled	Target group	Definition of OMD—max. No. of involved:		Arms	Brain mts	Primary outcome measures
				Lesions	Organs			
NCT02089100 (STEREO-SEIN) randomized	3	Yes	MBC HR (+) HER2 (−)	5 (10 cm/7 cm or 500 mL)	NA	1. SBRT (all mts) + ST 2. ST	No	PFS
NCT01646034 (Oligo) randomized	3	Yes/No	MBC HR (+)/(−) HER2 (−)	3	NA	1.Intensified alkylating CT (CBDCA, thiotepa, CTX) with PBPC-reinfusion 2. CT × 3 (DOC, DOX, CTX, CBDCA, PAC, GEM)	NA	Event free survival
NCT02364557 randomized	2/3	Yes	MBC	2 (5 cm)	2	1. SOC (ST) 2. SBRT and/or Surgery + ST	No	PFS, OS
NCT02759783 (COMET) randomized	2/3	Yes	Stage IV BC, NSCLC prostate cancer	3	2	1. SOC 2. SBRT + SOC	No	PFS
NCT01446744 (SABR-COMET) [58] randomized	2	Yes	Metastatic tumors	5	NA	1. SOC 2. SBRT + SOC	Yes[a]	OS
NCT00929214	2	NA	MBC	3	1 (bones)	ST + Surgery and/or RT	No	PFS
NCT02581670 prospective non-randomized	2	NA	MBC	4 (< 5 cm)	2 (liver, lung)	SBRT	No	Toxicity, LC
NCT02206334	1	Yes	Stage IV: Various	4	NA	SBRT	No	DLT, AEs
NCT01706432 (BEAM ON)	Pilot study	Yes	MBC	5 (max 10 cm or < 500 cc)	NA	SBRT/SRS	Yes	CTCs
NCT01875666 randomized	0	NA	I–IV BC	NA	NA	Surgery → 1.T 2.P 3.T + P 4.T + L	NA	Difference in kinome activation pre and post treatment

OMBC oligometastatic breast cancer, *OMD* oligometastatic disease, *mts* metastases, *MBC* metastatic breast cancer, *HR* hormone receptors, *NA* not applicable, *SBRT* stereotactic body radiotherapy, *ST* systemic treatment, *PFS* progression-free survival, *CT* chemotherapy, *CBDCA* carboplatin, *CTX* cyclophosphamide, *PBPC* peripheral blood progenitor cell, *DOC* docetaxel, *DOX* doxorubicin, *PAC* paclitaxel, *GEM* gemcitabine, *SOC* Standard of Care, *NSCLC* non-small cell lung cancer, *OS* overall survival, *RT* radiotherapy; *LC* local control, *DLT* dose-limiting toxicity, *AEs* adverse events, *SRS* stereotactic radiosurgery, *CTC* circulating tumor cells, *BC* breast cancer, *T* trastuzumab, *P* pertuzumab, *L* lapatinib.

[a]Patients with 1–3 brain mts and no disease elsewhere (should not be randomized but treated with stereotactic radiotherapy);

Discussion

Despite that, MBC is considered as incurable disease there is a group of long-term survivors. Besides the still unknown biology and genetic changes which are apparently partly responsible for this state there are recognized some clinical features of this group: younger age, lower tumour burden and better performance status with long DFI [48, 59]. Therefore, it is believed that inducing CR particularly in OMD patients could lead to long-term responses and potentially be curative. The aggressive approach by combining local treatment and systemic therapy was proposed. It is claimed that removing all metastases can eliminate the source of newly changed clones with probably different metastatic potential and makes remaining tumour cells more sensitive to systemic treatment [21, 60]. The similar results were reported using either surgery (usually better results with R0) or ablative radiotherapy (usually better results when 1 metastatic lesion involved) [5, 30]. Although, results from direct comparison are not available, they are currently accepted alternatives. Surgery allows for tissue histopathological analysis and can be repeatable. In some situations, e.g. comorbidities, unresectable lesions or lack of consent, surgery could be replaced by SBRT with a different profile of side effects. It usually cannot be repeatable but using high-dose radiotherapy an additional abscopal effect can be achieved and immune response can play a very important role regarding outcomes in this group of patients [61]. SBRT appears to offer an excellent local control rates of approximately 80% (Table 1). It seems that concurrent aggressive local therapy with systemic treatment (time and sequence should be determined) for OMD can spare the need for long-lasting systemic therapy, time, can postpone disease progression or will be potentially curative. But this is a theory.

Doubt exist. We cannot be sure that the disease would not have the same scenario without aggressive approach and perhaps excellent outcomes are the result of indolent, slow progressing nature of OMD, usually detected accidentally. In Nguyen et al. study, women with limited disease had better outcomes than with extensive disease [27]. Also, in the literature we can find data that metastasectomy do not improve survival [62].

Most of the data are available from retrospective, non-controlled, single arm, limited by number of patients studies conducted in highly selective cohorts. Moreover, even comparison between studies dedicated only to SBRT in OMD is difficult. Mostly because of using different definition of OMD, sometimes involving patients with metastases limited to specific organs, application of different radiation doses (ablative/not ablative?), different tumour biology (favorable/not favorable) and related with that diversity of systemic treatment. Also patients with metastases fulfilling the criteria for operation could constitute a selected group with a favorable natural history.

Results from randomized phase III studies are needed. If they will confirm the assumptions of improving survivals, a new follow-up guidelines for early detection of "potentially curable" OMD cases will be needed. Nowadays, European Society for Medical Oncology do not recommend active surveillance imaging for earlier detection of metastases in asymptomatic BC patients [1]. OMD is more likely to be found during incidental or screening. When waiting for symptoms, the percentage of metastatic disease as limited is significantly decreasing [27, 28]. It is supported by data from Nguyen et al. and Dorn et al. study where OMD in patients with symptomatic and asymptomatic disease was found in 14.5% and 26.7% cases, respectively [28]. BCMetPats study to evaluate the usefulness of early detection of oligometastases by PET-CT, CT and MRI in women with high-risk BC (> 30%) for developing metastatic disease is underway [57].

Consequently, changing the surveillance will lead to detect truly OMD and disease with highly polimetastatic potential on its early phase. The first is the target for aggressive treatment. Biomarkers (e.g. miRNA, oligometastatic genotype) are needed to distinguish these cohorts [63]. The role of microRNA-200c in regulating oligometastatic to polymetastatic progression in the L1-R2-435-GFP xenograft model has been investigated [63].

Although, current data are encouraging we still need outcomes from randomized clinical trials (RCTs) to change the applicable guidelines. Furthermore, without knowing the benefit, the cost-effectiveness calculations are impossible. Despite that, local ablative treatment (surgery/SBRT) with systemic therapy in OMBCD is present justified for a very carefully selected group. Because for them with already favorable nature of their disease, aggressive treatment has greater chances to improve survivals and be carried out with the intention of cure. Currently, the appropriate candidate would be a young woman with good performance status, low tumour burden, and with long DFI. Decision should be made individually.

Conclusions

First, homogeneous definition of OMD is needed. Based mainly on tumour burden and course of the disease rather than only on strict number of metastatic lesions. Second, confirmation and strong evidence of improving outcomes by adding local treatment to systemic therapy is necessary from randomized, phase III clinical trials. Third, confirmation or modification of the most appropriate target group (RCTs). Fourth, define the most useful diagnostic tools for surveillance and finally after fulfilling all aforementioned

conditions changes in guidelines for follow-up and treatment will be necessary.

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Compliance with ethical standards

Conflict of interest Author declares that she has no conflict of interest.

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