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COMMENTARY

International Guidelines for Management of Metastatic Breast Cancer: Can Metastatic Breast Cancer Be Cured?

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A distinctive subset of metastatic breast cancer (MBC) is oligometastatic disease, which is characterized by single or few detectable metastatic lesions. The existing treatment guidelines for patients with localized MBC include surgery, radiotherapy, and regional chemotherapy. The European School of Oncology–Metastatic Breast Cancer Task Force addressed the management of these patients in its first consensus recommendations published in 2007. The Task Force endorsed the possibility of a more aggressive and multidisciplinary approach for patients with oligometastatic disease, stressing also the need for clinical trials in this patient population. At the sixth European Breast Cancer Conference, held in Berlin in March 2008, the second public session on MBC guidelines addressed the controversial issue of whether MBC can be cured. In this commentary, we summarize the discussion and related recommendations regarding the available therapeutic options that are possibly associated with cure in these patients. In particular, data on local (surgery and radiotherapy) and chemotherapy options are discussed. Large retrospective series show an association between surgical removal of the primary tumor or of lung metastases and improved long-term outcome in patients with oligometastatic disease. In the absence of data from prospective randomized studies, removal of the primary tumor or isolated metastatic lesions may be an attractive therapeutic strategy in this subset of patients, offering rapid disease control and potential for survival benefit. Some improvement in outcome may also be achieved with optimization of systemic therapies, possibly in combination with optimal local treatment.

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Metastatic breast cancer (MBC) is a heterogeneous disease that has a variety of different clinical scenarios, ranging from solitary metastatic lesions to diffuse and multiple organ involvement. Overall, survival of patients with MBC is slowly but steadily improving (1)—the risk of death is decreasing by 1%–2% each year (2). The greatest improvement is most probably related to the development and widespread availability of modern systemic therapies (3). In addition, modern diagnostic tools allow the detection of early metastatic disease, which may be more responsive to treatment than late metastatic disease (4,5). However, earlier diagnosis of metastatic disease may also result in a lead time bias, falsely increasing the survival times of these patients (2).

A distinctive subset of MBC patients who are most likely to gain substantial benefit from an intensified multidisciplinary therapeutic approach is represented by "oligometastatic" disease, which is characterized by solitary or few detectable metastatic lesions that are usually limited to a single organ. This population of "potentially curable" stage IV disease is estimated to be 1%–10% of newly diagnosed MBC patients (6). The existing guidelines (National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines in Oncology, European Society for Medical Oncology [ESMO] Clinical Recommendations) list surgery, radiation, and regional chemotherapy as possible therapeutic options in patients with localized metastatic disease (7,8).

The European School of Oncology–Metastatic Breast Cancer (ESO–MBC) Task Force addressed the management of these patients in its first consensus recommendations, stating: "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. A more aggressive and multidisciplinary approach should be considered for these selected patients. A clinical trial addressing this specific situation is needed" (9).

At the European Breast Cancer Conference (EBCC)-6, held in Berlin in March of 2008, the second public session on MBC guidelines addressed the controversial issue: "Can metastatic breast cancer be cured?" Historically, such an approach was not considered worthwhile because most patients' disease subsequently recurred because of undetected additional microscopic metastatic foci. The promising results of recent series of MBC patients undergoing "curative" surgery or radiotherapy both for primary tumor and distant metastases and the long-term survival achieved with modern systemic therapies raised justified interest and renewed the discussion on this complex topic. However, the value of such strategies has not been tested in prospective randomized trials and is not well recognized. In this commentary, the available data supporting the local (surgery and radiotherapy) and chemotherapy options, possibly associated with cure in MBC, are presented and discussed in detail.

Identification of MBC Patients Suitable for Curative Treatment

The unpredictable clinical behavior of MBC reflects the biological heterogeneity of the disease. The major task is therefore to identify predictive and prognostic models facilitating the selection of patients likely to benefit from curative options.

The development of modern technologies has enabled scientists to further classify breast tumors by measuring differences in thousands of biological pathways simultaneously. Gene expression profiling may identify tumors that are likely to metastasize, perhaps even the location of the metastases (10), and may identify predictive markers of sensitivity to different therapies. As a result, each patient would be offered an individualized treatment associated with the highest probability of therapeutic benefit (potentially leading to cure) and the smallest risk of resistance (11). Recent advances in pharmacogenetics may also allow the selection of the therapeutic options associated with the lower toxicity and higher therapeutic efficacy for the individual patient. In addition, improved diagnostic tools (such as positron emission tomography and detection of circulating tumor cells) (4,12) will possibly improve the identification of truly solitary metastatic lesions and/or minimal drug-resistant residual disease that is susceptible to effective local treatments (10).

Definition of Cure and Appropriate Endpoints

Most trials in MBC have relatively short follow-up. Long-term surveillance (>3–5 years) is exceptional, so little is known about the definitive outcome and the exact proportion of long-term survivors.

Complete response (CR), as assessed by conventional or modern imaging, and long-term progression-free survival have usually been used as surrogates for cure in MBC. However, with the advent of new technologies, we are now able to detect minimal residual disease, which may influence the definition of cure.

Long-term survival may simply reflect the indolent nature of the disease, rather than the impact of therapy. However, "cure" does not necessarily mean destroying every cancer cell, but rather rendering the disease harmless (without clinically significant adverse effects) for prolonged periods (13), which often can be achieved with less toxic therapies such as hormonal or targeted agents. Other clinical endpoints, such as tumor response, disease control, or time to progression are often used to replace overall survival (OS) in the ability to assess the long-term benefit of selected treatment strategies (14,15). Importantly, the ultimate goal in MBC management is to prolong the duration of life while maintaining a good quality of life. New endpoints must therefore be defined to assess this global definition of cure.

The Role of Systemic Treatment

Many reports from prospective clinical trials examine the effects of endocrine, cytotoxic, targeted, or combination treatments in MBC. Despite initial response, most patients develop progressive disease within 12–24 months, the median survival of endocrine nonresponsive or resistant MBC is 18–24 months, and less than 5% of patients live 5 years.

However, some patients who achieve a CR remain free of overt disease for prolonged periods, sometimes even beyond 20 years (16,17). These long-term survivors are usually young and have good performance status and limited metastatic disease. Although this fraction represents a minority of patients (between 1% and 3%), this finding challenges the common belief that MBC is universally fatal and raises the question of curability of this disease. In this regard, the oncology community is often divided in apparently opposite attitudes. On one side, there are those who believe that all patients deserve the most intensive treatment available, even if asymptomatic and at any cost of side effects, to offer them the small chance of achieving a durable CR. On the other side, there are those who believe that only palliation can be offered to these patients because MBC is virtually incurable. A more balanced view is a quality of life–oriented approach, choosing personalized treatments with a reasonable risk to benefit ratio and taking into account the patient's own attitude in guiding them toward more or less intensive therapy.

Recent therapeutic developments, such as the introduction of new cytotoxic agents (taxanes, vinorelbine, capecitabine, gemcitabine, liposomal anthracyclines, etc), newer hormonal agents, (third-generation aromatase inhibitors and fulvestrant), and biological therapies (trastuzumab, lapatinib, and bevacizumab), have resulted in constant improvements in treatment efficacy and consequently in MBC outcome (16).

An OS improvement was shown in two recent cohorts of patients with MBC as compared with the previous 20 years (2,3). In a population-based study of 2150 patients from British Columbia (3), women treated in 1999–2001 had a statistically significantly better survival than those treated in 1997–1998 (median of 667 days and 564 days, respectively), and both cohorts had statistically significantly better survival than those treated in 1991–1992 and 1994–1995 (median of 438 days and 450 days, respectively). The greatest differences in survival in the latter two cohorts were attributed to the introduction of aromatase inhibitors, taxanes, and trastuzumab. The question remains in how many patients, these improvements would actually translate into cure.

Most data on long-term survival in MBC come from consecutive studies conducted at the University of Texas MD Anderson Cancer Center. In a series of 1581 patients treated with consecutive first-line standard-dose doxorubicin and alkylating agent combinations between 1973 and 1982, 263 (16.6%) patients achieved a CR and 49 (3.1%) remained free of disease for more than 5 years (18). After a median follow-up of 191 months, 26 patients (1.5%) remained in first CR and four patients died in CR after 118–234 months. A substantial decrease in the risk of progression was observed after approximately 3 years from initiation of therapy, dropping to a sustained 2% after 4 years, thus, stressing the need of long-term follow-up in MBC. The number of metastatic sites was lower in patients with long-term CRs than in the total patient population or in the total CR group. The CR rate was similar in patients with estrogen receptor (ER)-positive (14%) and ER-negative tumors (11%), but patients with ER-positive disease had, overall, statistically significantly better progression-free survival and OS (19). Another series of 438 patients treated within nine prospective randomized trials reported that, overall, of 49 (11%) patients achieving a CR, only one (0.2%) enjoyed a long-term CR (20).

Most first-line MBC patients in the historical studies had not received any previous chemotherapy (18–20). Compared with them, patients in modern series mostly relapse following adjuvant chemotherapy and unfortunately demonstrate lower response and survival rates (21).

The extensive literature available on first-line randomized clinical trials with modern drugs and/or combinations has shown overall statistically significant improvements in response rates, but few studies have found clear survival benefits, and usually no data are provided on the proportion of long-term survivors. Any potential impact of first-line therapies on OS may also be confounded by the effects of subsequent effective therapies; when testing new drugs and/or treatment strategies, efforts to identify survival surrogates have yielded discordant results and have not produced a validated tool to predict the long-term effects of chemotherapy in MBC (14,15,22–26).

Particularly interesting is the new scenario of potential long-term disease control with targeted therapies. Because the duration of clinical experience with targeted agents is relatively short (trastuzumab received Food and Drug Administration approval in 1998), few data exist on long-term outcomes of patients who are treated with these compounds. Published case reports suggest, however, that at least in a small subpopulation of patients, long-lasting remission can be achieved with these agents (27).

In conclusion, an increasing number of randomized clinical trials document statistically significant improvements in disease control with modern chemotherapy in MBC. In addition, a small but recognizable subset of patients achieve long-term remission.

Is There a Role for High-Dose Chemotherapy?

Several trials have tested the hypothesis that high-dose chemotherapy (HDC) with autologous bone marrow or peripheral stem cell transplantation may improve survival in women with MBC. The last Cochrane systematic review (28), published in 2005, examined six randomized controlled trials comparing the effectiveness of HDC (438 patients overall) with conventional chemotherapy (412 patients). No statistically significant difference in OS was shown between the high-dose and the control groups at 1, 3, or 5 years, despite a statistically significant difference in event-free survival favoring the high-dose group at 1 and 5 years of follow-up. In conclusion, due to the severe toxicity of HDC and the absence of a proven benefit, the final recommendation was to avoid the high-dose strategy outside of clinical trials (28). The recent randomized trials also confirmed, in unselected patient populations, the lack of a benefit from HDC either up front or as consolidation after response to standard induction chemotherapy (29–35).

"Adjuvant" Systemic Therapy After Local Treatment

The role of adjuvant systemic therapy after local treatment of solitary metastases (surgical resection or radiation therapy) has been investigated in many nonrandomized trials. The addition of systemic therapy is based on the assumption that micrometastases exist in the majority of these patients and might be eradicated in at least some of them.

The largest experience with adjuvant systemic therapy after local treatment of single distant metastases comes from a series of consecutive trials including 285 patients (the majority of whom had locoregional recurrence alone) conducted at the MD Anderson Cancer Center (36–39). In the three "anthracycline-based" trials, 20-year disease-free survival (DFS) and OS reached 26%, confirming the possibility of achieving a long-term disease control. Among the 53 patients with distant metastases, 12 (23%) achieved long-term disease control (6). In the newer "docetaxel-based" trial, among 26 patients (12 of whom had only locoregional relapse), 5-year DFS and OS were 34% and 59%, respectively, with less favorable results in the subgroup with distant metastases (6). In these trials, a simultaneous control group with no chemotherapy was not considered appropriate, and the results were compared with historical data from the same institution, which showed a 15-year DFS rate of only 3%.

Limited data exist on the use of HDC as adjuvant treatment after radical local therapy of oligometastatic breast cancer. In a series from the University of Colorado, 60 patients (18 with locoregional recurrence only) underwent HDC with autologous stem cell transplantation after curative local treatment. Relapse-free survival and OS at 5 years were achieved by 52% and 62% of patients, respectively (40). In a subgroup of patients with distant metastases only (without concomitant locoregional recurrence), the 5-year relapse-free survival was 59%. Importantly, the trial excluded patients with brain or liver metastases, whereas patients with limited bone marrow involvement were included. HER2 overexpression, number of metastatic sites, and axillary nodal ratio (number of positive nodes divided by number of sampled nodes) were reported as independent outcome predictors, suggesting a possible prognostic model for relapse after HDC (41). Selection bias, limited number of patients, and lack of validation of the proposed model in a different larger patient population prevent making any definite conclusions regarding the contribution of this treatment strategy to outcome.

In conclusion, available data suggest that, despite important differences in patient characteristics and selection bias, at 5 years after local treatment for a locally recurrent or metastatic lesion followed by adjuvant systemic treatment, 36%–52% of patients remain alive and without evidence of relapse.

The utility of chemotherapy after locoregional treatment for isolated locoregional recurrence (ie, not associated with distant metastases) is still an open question being currently investigated in a joint study by the International Breast Cancer Study Group (IBSCG) and the National Surgical Adjuvant Breast and Bowel Project (NSABP), under the umbrella of the Breast International Group (BIG).

Regional Chemotherapy

The ability to deliver higher concentrations of cytotoxic drugs to isolated tumor sites makes regional chemotherapy a possible alternative in patients with single metastatic foci, especially if not amenable to other local treatments. Small case series of regional hepatic intra-arterial therapy in patients with isolated liver metastases from breast cancer have been reported (42–45). Tumor shrinkage can sometimes be dramatic and may render patients candidates for liver resection with curative intent, potentially resulting in long-term DFS (46).

The Role Of Local Treatment

Surgery for Primary Tumor in the Presence of Metastatic Disease

MBC at diagnosis constitutes 3.5%–7% of all new breast cancers (46); this apparently marginal problem involves about 7000 new patients every year in the United States alone, up to 50% of whom have locally operable (T1–T3) primary tumors (47). Traditionally, this group of patients was managed primarily with systemic modalities, limiting local treatments to palliative management of uncontrolled local and/or regional disease (in form of so-called "toilette mastectomy" or low-dose radiotherapy).

The biological rationale for removing the primary tumor in case of proven disease dissemination is debatable. Several potential advantages have been proposed. By removing the primary tumor, one of the sources of further metastatic spread is eradicated (48–52); this risk of reseeding is more relevant with the current improvements in systemic treatments (53). Data from animal studies suggest that removal of tumor bulk may restore immunocompetence (54) because the primary tumor seems to modulate the immune system through release of immunosuppressive factors (55). A reduction in the number of cancer cells may also lead to increased efficacy of systemic therapy by decreasing the risk of emergence of chemoresistant cells and by removal of necrotic tumor tissue poorly accessible to drugs (54). Debulking surgery has been proven clinically effective in other common solid tumors, such as ovarian, colorectal, gastric, renal cancers, and malignant melanoma (56–58).

However, some potential disadvantages of removing the primary tumor have also been proposed. Because the primary tumor is a source of antiangiogenic factors and growth factor inhibitors, there may be an accelerated relapse in response to its removal (49,59); however, the rush of angiogenesis in distant disease sites may increase the chemosensitivity of malignant cells (60). The possible release of growth factors related to surgical wounding (51) and the immunosuppression caused by surgery and anesthesia (61) are also potential disadvantages.

Several series evaluated the role of local treatment for the primary tumor in patients with MBC at diagnosis (Table 1) (50,55,62,63,64,66). Importantly, in patients with positive surgical margins, surgery did not add any substantial survival benefit as compared with patients who did not undergo surgery.

Interestingly, the percentage of MBC patients undergoing surgery for the primary tumor in all these series is surprisingly high, ranging from 37% to 61.3% (49,50). These percentages reflect the ongoing change, despite the lack of randomized confirmatory data, in the perceived role of breast cancer surgery in the presence of metastatic disease. As already mentioned, the characteristics of MBC have changed and hence the comparison with historical controls and the applicability of old criteria for operability clearly needs reevaluation. Overall, patients undergoing surgery are more likely to be younger, with smaller endocrine responsive tumors and more often have only a single metastatic site without visceral involvement. Therefore, the benefit of surgery may, at least partially, be attributed to selection biases, such as surgical referral of patients with better general status, less advanced primary tumors, lower burden of metastatic disease, and better response to systemic treatment (49,53). The question is whether these patients lived longer because of tumor removal or had their tumors removed because of a predicted longer survival (67). A publication bias of reporting preferably the positive studies also cannot be excluded (49). Nevertheless, results of multivariable analyses, which control for these confounding factors, consistently suggest a survival benefit for optimal local treatment of the primary tumor. Many questions still remain unsolved, including which patients could benefit most from surgery and what is its optimal timing and the best systemic treatment for these selected patients (51,53,68).

In conclusion, there is a bulk of retrospective data suggesting the importance of local treatment of primary tumor and strongly recommending that well-conducted randomized trials are performed in this setting. One such trial is being developed under the joint effort of Breast International Group and the North American Intergroup. While waiting for data from these studies, surgery for breast primary tumor can be considered as a relatively inexpensive and low morbidity treatment, which can offer a rapid local control and has a potential for survival benefit, provided it is performed optimally.

Surgery for Lung and Liver Metastases

Several series have reported on lung and liver metastases resection in MBC (Tables 2 and 3): most data are from small series of patients collected over many years. The largest dataset comes from the International Registry of Lung Metastases and presents results of lung metastasectomy in 467 breast cancer patients (70). Complete resection was possible in 84% of patients and led to a median survival of 37 months (5-year OS = 38%, 10-year OS = 22%).

Identified prognostic factors for lung resection include disease-free interval and number of metastases (disease-free interval >36 months and solitary metastases being the most favorable), ER status, size of metastases, completeness of resection, and use of anatomical resection (as opposite to wedge resection) (69–71,72,74,76,77–79,81). Obviously, the reported data refer to a subset of patients who were selected for favorable prognostic factors, and any comparison with surgically untreated patients is threatened by serious biases.

Pulmonary resection in MBC patients, apart from its potential therapeutic value, is also an important diagnostic tool, especially in patients with a suspected first recurrence, allowing for differential diagnosis with second primary lung cancers and benign lesions (13,81). The proportion of lesions proved not to be breast cancer metastases in various series ranges from 7% to 66% (70,73–75,79,80,82,95,96). As the morbidity and mortality of pulmonary resection has decreased substantially over the last decades, this potentially beneficial procedure can be discussed in a selected group of patients (69–71,81).

Surgery to remove liver metastases is an accepted treatment modality in patients with colorectal cancer (97). Its role in breast cancer is, however, much less recognized. In various series of hepatic resection for breast cancer metastases, the reported median survival ranged from 14.5 to 63 months and the 5-year survival from 14% to 61%, in general, comparing well with nonsurgically treated patients. Most of the reported series, however, describe extremely selected patients, constituting 1% or less of MBC patients treated over the respective periods of time (83,88,90,98). As an

Table 1. Surgery for primary tumor in metastatic breast cancer patients*

First author (reference)	No. of patients: operated/all (%)	Median OS (mo)	5-y OS (%)	HR for OS (surgery vs not)	Prognostic factors (multivariable analysis)
Khan, 2002 (50)	9162/16023 (57.2%)	Total mastectomy: 31.9; partial mastectomy: 26.9; no surgery: 19.3	Margin (−): 35 (3y); margin (+): 26 (3y); no surgery: 17 (3y)	Margin (−): 0.61; margin (+): 0.75	Surgical resection/margin status, systemic treatment, No. of metastatic sites, site of metastases
Rapiti, 2006 (62)	127/300 (42%)	Adjusted BCSS: margin (−): 26†; margin (+): 17*; no surgery: 13†	BCSS: margin (−): 27; margin (+): 16; no surgery: 12	BCSS: margin (−): 0.6; margin (+): NS	Surgery for primary, age, method of diagnosis, regional N involvement, visceral or CNS metastases, hormonal treatment
Gnerlich, 2007 (55)	4578/9734 (47%)	Surgery: 27†; no surgery: 12*	Surgery: 24†; no surgery: 12†	0.63	Surgery, tumor size, tumor grade, year of diagnosis, use of RT
Blanchard, 2008 (63)	242/395 (61.3%)	Surgery: 27.1; no surgery: 16.8	Surgery: 22†; no surgery: 7*	0.71	Definitive surgery, ER status, PgR status, No. of metastases
Babiera, 2006 (51); Rao, 2008 (64)	82/224 (37%)	Not reached; predicted: 54	ND (median fu 32.1 mo)	0.5	Definitive surgery (trend), No. of metastatic sites, HER2 status
Fields, 2007 (52)	187/409 (45.7%)	Surgery: 26.8; no surgery: 12.6	Surgery: 28†; no surgery: 12*	0.53	Definitive surgery, site of metastases
Khan, 2003 (65)	5179/9197 (56.3%)	ND	Margin (−): 34.2 (3y); margin (+): 26.8 (3y); no surgery: 17.5 (3y)	0.67	Surgery with (−) margins
Carmichael, 2003 (66)	20/?	23	ND	N/A	ND

* BCSS = breast cancer–specific survival; CNS = central nervous system; ER = estrogen receptor; HR = hazard ratio; N = nodal; N/A = not applicable; ND = no data; NS = non-statistically significant; OS = overall survival; PgR = progesterone receptor; RT = radiotherapy.

† Data from survival curves.

example, in the series of Pocard et al. (86), all patients were asymptomatic and identified through intensive surveillance programs.

Interestingly, in contrast to lung metastases, where most of resected patients develop recurrence outside the lung or with disseminated disease, in case of hepatic resections, most recurrences occur in the liver (96). Repeated resection gives favorable results in some of these patients (83). Importantly, the selection criteria for surgery constitute favorable prognostic factors per se: consequently, the reported results need to be viewed with caution even though the safety of hepatic resection has improved during the last decades (89,96).

Radiofrequency ablation is a relatively new treatment modality that uses thermal energy to induce coagulation necrosis in tumor cells. Effective local control can be achieved in solitary lesions less than 3 cm in diameter; thus, this therapy provides

Table 2. Resection of pulmonary metastases from breast cancer*

First author (reference)	No. of patients	Median OS (mo)	5-y OS (%)
Friedel, 2002 (70)	467	35	35
Planchard, 2004 (69)	125	50	45
Friedel, 1994 (71)	91	ND	27
Murabito, 2000 (72)	62 (28 complete resection)	Complete resection: 79; incomplete resection: 15.5	Complete resection: 80
McDonald, 1994 (73)	60	42	37.8
Livartowski, 1998 (74)	40	70	54
Tanaka, 2005 (75)	39	32	30.8
Lanza, 1992 (76)	37	47	49.5
Staren, 1992 (77)	33	58 (single metastasis)	36
Girard, 1994 (78)	32	ND	ND
McCormack, 1978 (79)	28	20	15
Rena, 2007 (80)	27	ND	38
Ludwig, 2003 (81)	21	96.9	53
Mountain, 1978 (82)	21	27	14

* ND = no data; OS = overall survival.

Table 3. Resection of liver metastases from breast cancer*

First author (reference)	No. of patients	Median OS (mo)	5-y OS (%)
Adam, 2006 (83)	85	46†	41†
Pocard, 2001 (84)	65	ND	46 (4-y)
Elias, 2003 (85)	54	34	34
Pocard, 2000 (86)	52	42	65 (3-y)
Raab, 1998 (87)	34	27	18.4
Sakamoto, 2005 (88)	34	36	21
Vlastos, 2004 (89)	31	63	61
Yoshimoto, 2000 (90)	25	42†	33†
Elias, 1995 (91)	21	38.2†	24†
Ercolani, 2005 (92)	21	40.3	25
Singletary, 2003 (13)	21	40 (DFS)	55 (3-y DFS)
Pocard, 1997 (93)	21	ND	60

* DFS = disease-free survival; ND = no data; OS = overall survival.

† Since diagnosis of liver metastases.

promising survival rates in patients with no visceral extrahepatic disease or with single bone metastases (99,100,101). Local management of brain and bone metastases will be the subject of a separate manuscript.

In summary, available data demonstrate favorable results in a subset of patients undergoing "radical" local therapy for metastatic disease. Selection bias and the retrospective nature of available data do not allow for generalization of the results, and the use of such approaches must be individualized.

Conclusions

The presented data, overall, seem to suggest the possibility of a curative, multidisciplinary therapeutic approach for at least a fraction of patients with limited MBC. Definitive evidence from controlled prospective randomized trials is missing; available data are coming essentially from retrospective series, most with relatively few patients enrolled.

Because patients who are potentially eligible for this therapeutic strategy represent only 1%–3% of the total MBC population, a large global collaboration is needed to confirm its impact on long-term survival or cure and to ensure adequate statistical power and strength of the results. Enrolled patients must have comparable clinical and biological characteristics, extent of staging, and frequency of monitoring to avoid selection biases and stage migration, which can substantially affect the outcome.

The clinical consequences of confirming this hypothesis would be considerable. First, it would suggest that a selected subset of MBC patients should be approached with curative, not palliative, intent. Second, the current minimalistic postoperative monitoring should be revised to allow early diagnosis of low-burden disease relapse. The crucial issue of follow-up and its consequences will be addressed in detail by the Task Force in a separate manuscript. As a consequence, a rigorous economic evaluation would also be required to calculate the cost to benefit ratio and the assessment of personal and social impact of this shift in the management of MBC patients.

New predictive markers of sensitivity to selected therapies and innovative evaluation criteria to assess long-term treatment efficacy will be the essential prerequisites to address the biological complexity and heterogeneity of MBC. The ultimate goal is to optimize the efficacy of individualized therapeutic strategies.

Very importantly, all available treatment options should be discussed with the individual patient with a clear explanation of the risk to benefit ratio. It is also important to recognize that the definition of "breast cancer survivor" has evolved and is subject to different interpretations. In the past, survivor was almost exclusively used to describe someone who was free of disease 5–10 years after diagnosis. More recently, it has become a dynamic concept that affirms the potential for quality living after a breast cancer diagnosis, therefore also including maximizing health and well-being if recurrence occurs and while living with metastatic disease.

Based on the available data, the ESO–MBC Task Force retains its original recommendation statement: "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. A more aggressive and multidisciplinary approach should be considered for these selected patients. A clinical trial addressing this specific situation is needed."

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Notes

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