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Improvement of survival and prospect of cure in patients with metastatic breast cancer

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Abstract

Patients with metastatic breast cancer have traditionally been considered incurable with conventional treatment. However, 5–10% of those patients survive more than 5 years, and 2–5% survive more than 10 years. Recent studies suggest that the survival of patients with metastatic breast cancer has been slowly improving. In this review, we examine the possible curative approach for a certain group of patients with metastatic breast cancer. We identify that patients most likely to benefit from such an aggressive approach are young and have good performance status, adequate body functional reserve, long disease-free interval before recurrence, oligometastatic disease, and low systemic tumor load. An aggressive multidisciplinary approach including both local treatment of macroscopic disease and systemic treatment of microscopic disease can result in prolonged disease control in certain patients with metastatic breast cancer. Whether patients with prolonged disease control are “cured” remains controversial.

Keywords

Metastatic breast cancer; Chemotherapy; Targeted therapy; Radiation therapy; Surgery

Introduction

Breast cancer is the most common cancer among women in the USA, where it is estimated that breast cancer will account for 207,090 new cancer cases in 2010. In terms of cancer-related mortality, breast cancer is ranked second among women in the USA, where it is predicted to cause 39,840 deaths in 2010 [1]. The favorable survival outcome in breast cancer is mainly due to two factors: (1) detection of disease at an early stage with screening mammography, which is in common use, and (2) advances in adjuvant systemic treatment—including chemotherapy, hormone therapy, and HER2-targeted therapy—that eliminates micrometastases after definitive breast cancer surgery. Unfortunately, it is estimated that about 30–50% of patients with early to locally advanced breast cancer at diagnosis have relapses despite the use of adjuvant systemic treatment after surgery. In addition, about 5–10% of patients with breast cancer present with metastatic disease at diagnosis.

Patients with metastatic disease at either initial diagnosis or relapse have traditionally been considered incurable with conventional treatment. However, although the median survival of patients with metastatic breast cancer who undergo treatment is only 24 months, 5–10% of those patients survive more than 5 years, and 2–5% survive more than 10 years [2, 3]. Furthermore, over the past decade, the survival of patients with metastatic breast cancer has been slowly improving. Giordano et al. [4] analyzed the survival data of 834 patients with metastatic recurrent breast cancer treated between 1974 and 2000 at MD Anderson Cancer Center. All patients were treated with anthracycline-based chemotherapy. The results showed a trend toward an association between later year of recurrence and improved survival, with a 1% reduction in risk per year. Chia et al. [5] found a similar survival improvement by year in 2,156 patients with metastatic recurrent breast cancer treated in British Columbia between 1991 and 2001. Potential reasons for this improvement in survival among patients with metastatic breast cancer are new systemic chemotherapy agents; the identification of new cancer pathway targets and development of new targeted therapeutic agents; and advances in technology that make it possible to identify patients with limited metastatic disease. Given the observed improvement in survival, it is now well accepted that certain patients with metastatic breast cancer could eventually be considered “cured” of disease as a result of the modern multidisciplinary treatment approach.

Definition of “cure”

Traditionally, cancer has been considered cured when the disease is totally eliminated from the patient and the patient has a normal life expectancy without the threat of recurrence [6]. However, even with the most advanced radiologic imaging or laboratory monitoring methods, it is not easy to be certain that cancer has been totally eliminated. Cancer presents with both macroscopic and microscopic disease. Even when macroscopic disease has been eliminated, microscopic disease can persist, as illustrated by the fact that cancer can recur after years of remission. However, if microscopic disease has no influence on the patient’s life expectancy or quality of life, then clinically speaking, there is no difference between microscopic disease and true cure. If one follows a strict definition of cure, a patient can be considered cured only when he or she has a normal life span and dies without any evidence of either macroscopic or microscopic disease (“true cure”). An alternative definition of cure would be that all macroscopic disease has been eliminated from the patient’s body and the patient has a normal life expectancy with all possible microscopic disease under control (“clinical cure”). Whether this “clinical cure” is truly meaningful for patients with metastatic breast cancer remains unknown.

Approach to potentially curative treatment in metastatic breast cancer

In patients with early-stage or locally advanced breast cancer, treatment is generally delivered with curative intent, and potentially curative treatment is multidisciplinary, involving combinations of local treatment (surgery and/or radiation therapy) and systemic treatment (chemotherapy and targeted therapy, including antiestrogen therapy and anti-HER2 therapy). Because metastatic breast disease is basically a systemic disease with both macroscopic and microscopic disease, systemic treatment is the main treatment in terms of controlling the disease. The distantly involved macroscopic disease in metastatic breast cancer traditionally precludes the use of local treatment except local symptomatic control such as pain control by radiation therapy. However, to potentially cure a metastatic breast cancer, a similar multidisciplinary approach will have to be considered. This potentially curative approach should include treatment of both macroscopic disease (with surgery and/or radiation therapy) and microscopic disease (with systemic chemotherapy and/or targeted therapy, including antiestrogen therapy and anti-HER2 therapy).

Macroscopic treatment in metastatic breast cancer

Although systemic treatment is effective against both macroscopic and microscopic disease, local treatment eliminates macroscopic disease more rapidly than systemic treatment, especially in patients with oligometastasis—that is, if the patient has only a solitary metastasis or only a few metastatic lesions, usually limited to a single organ. The organs most commonly involved in metastatic breast cancer, in decreasing order of frequency, are bone, lung, liver, and brain. Local treatment can eliminate all or most macroscopic disease so that systemic treatment can effectively control or even eliminate microscopic disease.

Pulmonary metastasis

About 10–25% of patients with metastatic breast cancer have lung involvement alone [7, 8]. Greenberg et al. [3] reported on 1,581 patients treated with combination chemotherapy for metastatic breast cancer, including 697 patients with lung or pleural metastases. The 5-year disease-free survival rate was only 2.4%. In contrast, studies of pulmonary metastasectomy in patients with metastatic breast cancer (1,058 patients total) show median survival durations from 32 to 96.9 months and 5-year survival rates from 27 to 80% (Table 1) [7–18]. The results of these studies also suggested that in patients with a solitary pulmonary metastasis, complete versus incomplete metastasectomy and long disease-free interval before pulmonary metastasis predicted better outcome [14].

Hepatic metastasis

Unlike liver involvement in metastatic colorectal cancer, liver involvement in metastatic breast cancer is usually a late development and signifies the end of the natural course of disease. The prognosis associated with liver metastasis in breast cancer is much worse than that associated with liver metastasis in colorectal cancer. About half of patients with metastatic breast cancer have liver involvement during their disease course, and about 5–12% of patients with metastatic breast cancer have liver involvement only [19–21].

Multiple studies of hepatic metastasectomy in metastatic breast cancer (602 patients total) have been reported (Table 2) [22–45]. The results showed median survival durations from 15 to 63 months and 5-year survival rates from 12 to 61%. The results also suggested that in patients with a solitary hepatic metastasis, normal hepatic reserve and long disease-free interval before hepatic metastasis predicted better outcome [30, 32].

Other local therapies for hepatic metastasis include radiofrequency ablation, cryotherapy, percutaneous ethanol injection, interstitial laser therapy, hepatic arterial infusion, and transarterial chemoembolization. All of these local therapies are well studied in patients with metastatic colorectal cancer with hepatic oligometastasis and in patients with unresectable primary hepatocellular carcinoma. However, the use of nonsurgical local therapies in patients with metastatic breast cancer with hepatic oligometastasis has been limited (Table 3) [46–59]. In general, the results with nonsurgical therapies are inferior to those with hepatic metastasectomy. However, a combination of nonsurgical local therapy and surgical resection may provide a better outcome than either approach alone.

Brain metastasis

Like hepatic metastasis, brain metastasis is a late event in the natural course of breast cancer. The prognosis of breast cancer patients with brain metastasis is poor; the prognosis is especially poor in patients with multiple lesions, leptomeningeal involvement, or uncontrolled systemic disease. About 10–16% of patients with metastatic breast cancer have brain involvement during their disease course, but fewer than 5% of patients with metastatic breast cancer have brain involvement only [60–63].

Whole-brain irradiation is the standard of care for brain metastasis, but for patients with a single brain metastasis, surgical resection plus whole-brain irradiation provides better median survival: 28 months compared with 14–16 months for patients treated with whole-brain irradiation alone (Table 4) [64–67]. The strongest predictor of better outcome is a lack of uncontrolled systemic disease.

Stereotactic radiosurgery has the advantage of avoiding the general central nervous system toxic effects of whole-brain irradiation. Stereotactic radiosurgery can also be used for brain lesions that are not easily accessible with standard surgery or for lesions that recur after surgical resection or whole-brain irradiation. Several studies have reported a possible benefit in patients after stereotactic radiosurgery (Table 5) [68–73].

Bone metastasis

Bone is the most common organ involved in metastatic breast cancer. Bone involvement usually signifies an indolent course of disease [74, 75]. Patients with metastatic breast cancer who have only bone or soft tissue involvement usually do much better than patients with involvement of other organs. About 20% of patients with metastatic breast cancer present with bone involvement only [76]. Local radiation therapy is the standard of care, especially if the bone metastasis produces significant symptoms. However, patients with isolated sternal involvement may benefit from aggressive surgical resection (Table 6) [77–79].

Primary breast tumor

About 5–10% of patients with breast cancer present with metastatic disease at diagnosis. Because metastatic disease represents disseminated disease, systemic therapy is the most important component of therapy. However, there are several potential advantages of removing the primary tumor in metastatic breast cancer especially when the metastatic disease can be well controlled. First, removing the primary tumor eliminates the primary tumor as a potential source of further metastasis [80–84]. Second, removing the primary tumor may remove the source of growth factors that promote metastasis, which are believed to originate from the primary tumor [85]. Third, preclinical data indicate that removing the primary tumor may restore the immunocompetence of the host [86, 87]. Fourth, removing the primary tumor may decrease the tumor load significantly and render the subsequent systemic treatment more effective [86]. Multiple nonrandomized studies including more than 10,000 patients have examined the impact of removal of the primary breast tumor in patients with breast cancer with metastatic disease at diagnosis (Table 7) [80, 81, 84, 87–90]. The results revealed a significant survival advantage (hazard ratio for death 0.5–0.71). The most important prognostic factor is the status of the surgical margins. Patients with a positive margin after removal of the primary tumor will not benefit from the procedure.

The Eastern Cooperative Oncology Group (ECOG) is currently conducting a randomized phase III trial (E2108 trial) of the value of early local therapy for the intact primary tumor in patients with metastatic breast cancer. Eligible patients will receive standard systemic therapy for 16 weeks. Those who have clinical response or stable disease will be randomized into either continue systemic therapy or early local therapy. The primary objective is to evaluate whether early local therapy of intact primary disease in patients with stage IV breast cancer whose disease does not progress during initial optimal systemic therapy will result in prolonged survival, compared with patients who continue on systemic therapy.

Microscopic treatment in metastatic breast cancer

Local treatment is used to eliminate macroscopic disease in metastatic breast cancer with oligometastasis. However, without systemic treatment, microscopic disease will eventually

become macroscopic disease. Therefore in patients with metastatic breast cancer being treated with curative intent, systemic treatment remains the most critical treatment component. The goal of the systemic treatment is either a total elimination of all disease (the aforementioned “true cure”) or continued suppression of all disease (the aforementioned “clinical cure”).

Currently, systemic treatment options in breast cancer include cytotoxic chemotherapy, antiestrogen therapy, and anti-HER2 therapy. With advances in the identification of different targets in the breast cancer pathway, additional target-specific therapies will become available.

Successful control of microscopic disease is the key to potential cure in patients with metastatic breast cancer. Greenberg et al. [3] showed that achievement of an initial complete response after standard-dose chemotherapy was associated with prolonged progression-free survival and overall survival. In patients with chemotherapy-naïve metastatic breast cancer, standard-dose chemotherapy can produce complete response rates of 15–19% and overall response rates of 63–67%. The response typically lasts about 12 months, but some patients (usually fewer than 5%) remain progression-free at 5 years after treatment. The importance of systemic treatment in metastatic breast cancer is also demonstrated by MD Anderson data presented by Rivera et al. [91]. Forty-five patients with metastatic breast cancer received six cycles of anthracycline-based chemotherapy after undergoing local treatment to render them free of macroscopic disease. Compared with historical control patients who did not receive any chemotherapy after local treatment, the patients who received chemotherapy after local treatment had significantly better overall and disease-free survival.

High-dose chemotherapy with autologous hematopoietic stem cell transplantation

Most of the chemotherapeutic agents used in cancer management have demonstrated a dose-response relationship. Therefore, increasing the dose of chemotherapy might be expected to result in more tumor cells being killed. However, normal cells in the body, such as bone marrow cells, are also susceptible to the cytotoxic effects of high-dose chemotherapy. To address this dilemma, patients can be treated with high-dose chemotherapy in combination with hematopoietic stem cell transplantation. In this process, hematopoietic stem cells are collected from the patient and stored, high-dose chemotherapy is administered, and then the previously collected hematopoietic stem cells are infused back into the patient to restore the normal hematopoietic system.

Since the late 1990s, eight randomized trials of high-dose chemotherapy with autologous hematopoietic stem cell transplantation in metastatic breast cancer have been described [92–100]. Results from seven of these trials have already been published [92, 95–100], and for one trial, an updated report was also published after longer follow-up [93]. Results for the remaining trial have only been published in preliminary form [94]. Together, these eight trials enrolled more than 1,000 patients. Six trials showed a significant benefit in terms of progression-free survival but not overall survival. One trial, the PEGASE 04 study, showed a significant benefit in terms of both progression-free survival and overall survival (Table 8) [96]. In 2008, Berry et al. [101] presented the first meta-analysis using individual data from six of the eight trials; this analysis showed a significant benefit in terms of progression-free survival and a trend toward benefit in terms of overall survival. Subgroup analysis suggested that young patients (less than 50 years old) and patients with only soft tissue involvement will benefit from this treatment.

Selection of patients with metastatic breast cancer for potentially curative treatment

Currently, potentially curative treatment is generally considered in patients with metastatic breast cancer only if the disease is oligometastatic. Multiorgan involvement is usually considered a contraindication to potentially curative treatment except in patients with indolent lesions, like bone metastases, whose other sites of disease can be controlled locally with surgery and/or radiation.

Studies to date suggest that in addition to oligometastatic disease, there are several other features common to the patients who are most likely to benefit from a potentially curative approach: young age, good performance status, adequate body functional reserve, long disease-free interval before recurrence (in patients who do not have metastatic disease at presentation), and low systemic tumor load [102].

Conclusion

The current data suggest that in certain patients with metastatic breast cancer, an aggressive multidisciplinary approach including both local treatment of macroscopic disease and systemic treatment of microscopic disease can result in prolonged disease control. Whether patients with prolonged disease control are “cured” remains controversial. The patients most likely to benefit from such an aggressive approach are young and have good performance status, adequate body functional reserve, long disease-free interval before recurrence, oligometastatic disease, and low systemic tumor load. It is true that such patients have all of the features of an indolent disease and possibly may do well with or without an aggressive approach. Therefore, a well-designed prospective randomized trial is needed to determine the true benefit of such an aggressive curative approach. Outside of such a trial, it is reasonable to offer patients who meet the aforementioned criteria an aggressive multidisciplinary approach and the chance of cure. It is important to realize that metastatic breast cancer is not always a death sentence.

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Table 1

Survival in patients with metastatic breast cancer after pulmonary metastasectomy

Reference	No. of patients	Median survival (months)	5-year survival (%)
Staren et al. [9]	33	58	36
Lanza et al. [10]	37	47	49.5
McDonald et al. [11]	60	42	37.8
Friedel et al. [7]	91	–	27
Livartowski et al. [12]	40	70	54
Murabito et al. [13]	28	79	80
Friedel et al. [14]	467	37	38
Ludwig et al. [15]	21	96.9	53
Planchard et al. [8]	125	50	45
Tanaka et al. [16]	39	32	30.8
Rena et al. [17]	27	–	38
Yoshimoto et al. [18]	90	76	54

Table 2

Survival in patients with metastatic breast cancer after hepatic metastasectomy

Reference	No. of patients	Median survival (months)	5-year survival (%)
Schneebaum et al. [22]	6	42	–
Lorenz et al. [23]	8	15	12
Elias et al. [24]	21	26	22
Pocard et al. [25]	21	–	60
Raab et al. [26]	34	27	18.4
Seifert et al. [27]	15	57	54 (3-year survival)
Kondo et al. [28]	6	36	40
Yoshimoto et al. [29]	25	34	27
Selzner et al. [30]	17	25	22
Maksan et al. [31]	9	–	51
Pocard et al. [32]	65	47	46
Carlini et al. [33]	17	53	46
Singletery et al. [34]	21	40 (disease-free survival)	55 (3-year survival)
Elias et al. [35]	54	34	34
Arena and Ferrero [36]	17	41	–
Vlastos et al. [37]	31	63	61
d'Annibale et al. [38]	18	32	30
Ercolani et al. [39]	21	42	25
Okaro et al. [40]	6	31	–
Sakamoto et al. [41]	34	36	21
Adam et al. [42]	85	32	37
Martinez et al. [43]	20	32	33
Thelen et al. [44]	39	42	–
Caralt et al. [45]	12	33	36

Table 3

Survival in patients with metastatic breast cancer after nonsurgical therapy for hepatic oligometastasis

Reference	No. of patients	Survival
Radiofrequency ablation		
Livraghi et al. [46]	24	42% disease-free survival rate with median follow-up time of 19 months
Lawes et al. [47]	19	42% at 30 months
Gunabushanam et al. [48]	14	64% at 12 months
Sofocleous et al. [49]	12	30% at 5 years
Interstitial laser therapy		
Mack et al. [50]	232	Median survival of 14.5 months 5-year survival rate of 41%
HAI or TACE		
Fraschini et al. [51]	31	Median survival of 11 months
Arai et al. [52]	56	Median survival of 12.5 months
Yayoi et al. [53]	17	1-year survival rate of 50% with HAI 1-year survival rate of 44.4% with TACE
Ikeda et al. [54]	26	Median survival of 25.3 months
Gofuku et al. [55]	14	One patient disease-free at 76 months
Giroux et al. [56]	8	Median survival of 6 months
Li et al. [57]	48	3-year survival rate of 13%
Camacho et al. [58]	10	One patient disease free 48 months after HAI followed by surgery
Buijs et al. [59]	14	Median survival of 25 months

HAI hepatic arterial infusion, *TACE* transarterial chemoembolization

Table 4

Survival in patients with metastatic breast cancer after cranial metastasectomy

Reference	No. of patients	Median survival (months)	5-year survival (%)
Salvati et al. [64]	9	15	–
	25	28 ^a	–
Wronski et al [65]	70	14	–
Boogerd et al. [66]	28	23	–
Pieper et al. [67]	63	16	17

^a Cranial metastasectomy followed by whole-brain irradiation

Table 5

Survival in patients with metastatic breast cancer after stereotactic radiosurgery for cranial metastases

Reference	No. of patients	Survival
Firlik et al. [68]	30	Median survival of 13 months
Amendola et al. [69]	68	Median survival of 7.8 months 1-year survival rate of 32%
Lederman et al. [70]	43	Median survival of 7.5 months 2-year survival rate of 12.8%
Combs et al. [71]	62	Median local control interval of 9 months
Goyal et al. [72]	43	Median survival of 13 months
Akyurek et al. [73]	49	Median survival of 19 months

Table 6

Survival in patients with metastatic breast cancer after sternectomy

Reference	No. of patients	Median survival (months)	5-year survival (%)
Noguchi et al. [77]	9	30	–
Incarbone et al. [78]	9	–	48
Lequaglie et al. [79]	22	–	42

Table 7

Survival in patients with metastatic breast cancer after surgical removal of the primary tumor

Reference	No. of patients	Median survival (months)	5-year survival (%)	Hazard ratio (95% CI)
Khan et al. [80]	9,162	31.9	35 (3-year survival)	0.61 (0.58–0.65)
Carmichael et al. [88]	20	23	–	–
Rapiti et al. [89]	127	26	27	0.6 (0.4–1.0)
Babiera et al. [81]	82	–	–	0.5 (0.21–1.19)
Gnerlich et al. [87]	4,578	27	24	0.63 (0.6–0.66)
Fields et al. [84]	187	26.8	28	0.53 (0.42–0.67)
Blanchard et al. [90]	242	27.1	22	0.71 (0.56–0.91)

CI confidence interval

Table 8

Results of trials of high-dose chemotherapy with autologous hematopoietic stem cell transplantation in metastatic breast cancer

Reference	No. of patients	Progression-free survival (HDC vs SDC)	<i>p</i> value	Overall survival (HDC vs SDC)	<i>p</i> value
Stadtmauer et al. [92, 93]	184	4 versus 3%	0.3	14 versus 13%	0.6
Crown et al. [94]	110	29 versus 22%	0.047	NR	
Schmid et al. [95]	93	8.9 versus 9.3%	0.95	20.8 versus 18.2%	0.75
Lotz et al. [96]	61	18.7 versus 0%	0.005	36.8 versus 13.8%	0.029
Vredenburgh et al. [97]	100	25 versus 10%	<0.006	26.5 versus 38%	0.7
Vredenburgh et al. (bone only) [98]	69	17 versus 0%	<0.0001	17 versus 9%	0.1
Biron et al. [99]	179	27 versus 10%	0.0002	38 versus 30%	0.7
Crump et al. [100]	224	11 versus 9 months	0.006	37 versus 38%	0.4

HDC high-dose chemotherapy, NR not reported, SDC standard-dose chemotherapy