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From improved survival to potential cure in patients with metastatic breast cancer

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Metastatic breast cancer (MBC) is hard to cure by the therapies currently available and median long-term survival in MBC has been reported as either 18–24 months [1] or 2–4 years [2]. Even the definition of "cure" for MBC remains controversial. Some suggest that cure means that every single cancer cell should be eradicated, permitting a normal life span without threat of recurrence [3, 4]. Others, however, propose that cure does not necessarily mean destroying every cancer cell, but rather rendering the disease harmless (without clinically significant adverse effects) for prolonged periods [5]. As medians for survival periods in MBC patients are generally short, reports on prognosis of MBC longer than 3–5 years are extremely limited. The first evidence for poor long-term prognosis in MBC was reported by Greenberg et al. [6] and Rahman et al. [7] based on an observational study conducted from 1973 to 1982. This study assessed the outcome of 1,581 relapsing breast cancer cases treated with a combination regimen using anthracycline and alkylating agents as a first-line approach. Complete response (CR) rate was 16.6% and only 3.1% of the entire study population or 18.6% of those who achieved CR remained disease-free for more than 5 years. During the entire observation period (median approximately 16 years), only 1.6% of the total patents analyzed retained their CR status. Interestingly, in a nonselective population-based study cohort regarding long-term MBC survivals and their characteristics, 5 out of 149 (3.4%) MBC patients remained without evidence of relapsing disease for 9–14 years, 4 out of whom never received chemotherapy. This observation implied that aggressive use of strong chemotherapy regimes may not necessarily be a key factor for survival [4].

As we discussed above, though based on the limited reports, long-term prognosis for MBC is devastating. Have we, then, made any progress in treating MBC? Transition in the estimated survival of the MBC patients over the last century is summarized in Table 1. Between 1920 and 1980, combination drug programs have become available, yet may not have resulted in dramatic improvement in overall survival (OS) of the MBC patients [8]. OS observed between 1942 and 1975 also showed no significant prolongation of survival time in patients with MBC [9]. We had to wait till the twenty-first century for some hope of a cure to be reported, at least in a portion of the MBC patients [10–12]. In particular, since the introduction of doxorubicin to our clinical practice in mid-1970s, prognosis of MBC continued to improve, though more recent studies involving newer systemic therapy regimens are often focused on highly selected patient populations and therefore the effects of various biases are not negligible in such studies. Newer and more effective systemic agents for the treatment of MBC along with advances in supportive care, and the development of diagnostic technologies for the earlier detection of MBC are also accelerating our progress.

Such anticipation for improved outcome in MBC was further supported by the systematic review of 370 randomized trials (54,189 subjects in total) conducted between 1973 and 2007 with chemotherapy and/or targeted therapy [13]. The meta-analysis suggested that stepwise improvements of therapeutic efficacies either by chemotherapy or targeted treatments have cumulatively led, despite each observation period being relatively short, to major improvement in the tentative survival of patients with

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Table 1 Transition of the estimated overall survival of metastatic breast cancer since the early twentieth century

References	Study period	Treatment	Number of patients	OS		Statistical details
				Med. (M)	5Y (%)	
Todd et al. [8]	1920–1930	S ± R ± HT	21	21	7	
	1930–1940		40	30[a]	10[a]	
	1940–1950		82	35[a]	13[a]	
	1950–1960	CT	79	38[a]	15	
	1960–1970		168	42[a]	26	
	1970–1975		96		28[a]	
	1975–1980	DOX	88	43	25[a]	
Patel et al. [9]	1942–1950	S ± R ± HT	14	19[a]		
	1951–1955	CT	30	15[a]		
	1956–1960		53	22[a]		
	1961–1965		240	21[a]		
	1966–1970		82	20[a]		
	1971–1975		54	24[a]		
Giordano et al. [10]	1974–1979		93	15	10	Multivariate analysis: $P = 0.09$
	1980–1984		216	17	14	
	1985–1989		235	22	22	
	1990–1994		185	27	29	
	1995–2000		106	58	44	
Andre et al. [11]	1987–1993		343	23	11	1987–1993 versus 1994–2000: $P < 0.001$
	1994–2000	PAC	381	29	28	
Chia et al. [12]	1991–1992			14.3	33[b]	Total no. of patients 2,150
	1994–1995	PAC, VIN		14.8	34[b]	1991–1995 versus 1997–1998: $P = 0.002$
	1997–1998	AI		18.5	44[b]	1997–1998 versus 1999–2001: $P = 0.05$
	1999–2001	TRA, CAP		21.7	45[b]	

AI aromatase inhibitors, *CAP* capecitabine, *CT* chemotherapy, *DOX* doxorubicin, *HT* hormonal therapy, *M* months, *Med.* median, *OS* overall survival, *PAC* paclitaxel, *R* radiotherapy, *S* surgery, *TRA* trastuzumab, *VIN* vinorelbine, *Y* years

[a] Estimated from the readings of the Kaplan–Meier curves in the article

[b] Two-year survival rate

advanced breast cancer. Therefore, it is not illogical to assume that disease-free periods after achieving CR are also being prolonged.

Unfortunately, there is no doubt, at present, that long-term prognosis after treatment of MBC is, in general, poor. On the other hand, cases that remained disease free for over 20 years after the detection and treatment of MBC were reported. Factors that affect prognosis in MBC suggested in the literature are the numbers of sites of recurrence, tumor cell burden, patient's age and performance status (PS), post-surgical disease-free interval (DFI), and tumor biology (histological grade, estrogen receptor status, and HER-2 status) [3, 14]. The long-term survivors are usually young, with excellent PS, and have limited metastatic lesions [2]. CR is induced more often in MBCs with lower tumor burden, good PS, and predominance of metastases in soft tissues. Patients who have achieved CR demonstrate significantly longer survival compared with those who did not reach CR [1, 7, 15]. Among those factors, the involvement of a single or a few organs with the metastatic lesions, each of which generally is solitary, characterizes oligometastatic breast cancer (OMBC) [4, 5, 14, 16]. The concept of OMBC is a new paradigm proposed by Hellman and Weichselbaum [16], and suggests that patients with oligometastases, either de novo or following systemic treatment, could potentially be cured by ablation of these lesions, whereas more advanced metastatic disease will require more aggressive and effective systemic treatment. The term OMBC has now become synonymous with limited metastases, solitary metastasis, isolated metastases, or minimal metastases. However, OMBC is not yet sufficiently recognized. Some suggest that an aggressive approach with multidisciplinary treatment would be beneficial for potential long-term CR or even cure [1], whereas little evidence is available regarding outcomes of OMBC and their long-term prognosis.

In OMBC, surgical excision for both diagnostic and therapeutic purposes, and/or radiation therapies, is usually

performed, and consequent disease-free condition is determined as stage IV-NED (no evidence of clinical disease). The largest assessment for the longest period covering 30 years was conducted at the M.D. Anderson Cancer Center [17]. In this study, the authors analyzed results from four phase II trials with isolated recurrence cases (equivalent to OMBC) and effects of multidisciplinary treatment were evaluated in the subjects, who underwent curative surgery and/or irradiation for their recurrent lesions to induce stage IV-NED, followed by post-surgical adjuvant systemic therapy similar to a strategy for primary breast cancers. Median observation periods for the survivors till each last follow-up visit were 212.5 months ($N = 285$). Median OS time was 87 months. OS rates were 56, 42, and 26% for 5, 10, and 20 years, respectively, and median relapse-free survival (RFS) time was 42 months with RFS rates at 41, 34, and 26% for 5, 10, and 20 years, respectively. There were 28 (10.8%) cases that remained disease free for over 20 years. Considering the lack of comparative phase III trials testing the effects of chemotherapy versus watchful observation in subjects with stage IV-NED relapsing breast cancer, these results from the M.D. Anderson Cancer Center estimating 20-year RFS and OS as 26% would at best imply that clinical cure may have been achieved in those cases who remained in RFS for prolonged periods.

The European School of Oncology-Metastatic Breast Cancer (ESO-MBC) Task Force [5] stated that OMBC, which is characterized by solitary or a few detectable metastatic lesions that are usually limited to a single organ, is a distinct subset of MBC, and that our hope for a cure is most plausible in OMBC with an intensive multidisciplinary approach. Accordingly, the Task Force released guidelines that focus on the present situations and recommend therapeutic approaches for OMBC.

This special feature of *Breast Cancer* contains four review articles and one original article, addressing various aspects of the possibility of a cure for MBC. The specific topics include molecular-targeted agents aimed at eradicating breast cancer cells, and the roles of cancer stem cells; novel therapeutic agents for improved antitumor effects; advances in understanding of cancer cell biology such as molecular subtyping and possible individualized treatment strategy; perspectives in true cure and/or clinical cure and review of the outcome by local therapies; and the current view of long-term outcome in OMBC from our own experiences and literature review.

We have made significant advances in both diagnosing and treating MBCs. The former is most outstanding in our means of detecting microinvasive lesions early and accurately. The latter advances include various regimens for systemic treatment and methods of radiation therapy, as well as supportive care for undesirable effects of the main therapy. However, those advances have not yet successfully improved the outcome of MBC. Therefore, our expedition never stops and is anticipated to accelerate at the fastest speed ever. Special attention should be drawn to our approach in identifying and optimizing treatment strategy for OMBC, for which we are at a better position to achieve prolonged survival and even possible cure. To fulfill this goal, the evaluation of biomarkers that denote the molecular signature of OMBC is also critical. Our ambition will come true only by the dedicated efforts of each individual, i.e., both physicians and patients, and the insights gained from our experiences with OMBC should eventually be extended to the larger population of patients with MBC.

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