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EPIDEMIOLOGY

Survival of patients with de-novo metastatic breast cancer: analysis of data from a large breast cancer-specific private practice, a university-based cancer center and review of the literature

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Abstract Approximately 6 % of patients with breast cancer are diagnosed with de-novo distant metastases. We set out to look at two cohorts of patients seen at breast cancer-specific practices, compare the results to other reports and larger databases, and see how advances in treatment have impacted overall survival (OS). The records from a large breast cancer oncology private practice and a second data set from the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database were, retrospectively, reviewed to identify patients with de-novo metastases. We included those patients identified to have metastatic disease within 3 months of diagnosis of a breast primary cancer. Patients diagnosed between 1996 and 2006 were chosen for our study population. The OS for the private practice was 41.0 months (46.0 for ER positive and 26.0 for ER negative) and 36.0 months for UM/SCCC (52 months for ER positive and 36 months for ER negative). ER negativity and CNS- or visceral-dominant disease were associated with a significantly worse prognosis within the private practice. Dominant site was associated with a significantly worse prognosis within the UM/SCCC database but with a trend also for ER negativity. Age and ethnicity did not contribute significantly to the survival of patients within either cohort. The median survival in both cohorts and most other reported series was larger than that seen in the surveillance, epidemiology, and end results program and the National Cancer Database. The median OS among patients with de-novo metastatic breast cancer treated within two breast-specific oncology practices was over 3 years, which appears better than larger, more inclusive databases and publications from earlier decades.

Keywords De-novo metastatic breast cancer · ER · HER2 · Survival

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Introduction

With 231,840 projected new cases in 2015, breast cancer remains the most commonly occurring and second most lethal cancer among women in the United States [1]. Most patients present with localized disease, but as many as 6 % of patients present with de-novo metastases. Among this subset of patients, survival is considerably worse than in patients presenting with localized disease, but according to one study, may be better than in those with recurrent breast cancer [2]. Patients treated in the adjuvant setting with chemotherapy (but not endocrine therapy alone) fare worse upon systemic relapse than those with de-novo metastases. Patients with de-novo metastases have comparable overall survival (OS) to

those with systemic relapse >24 months from diagnosis of localized breast cancer but better survival compared to those with systemic relapse <24 months from initial diagnosis ([29.4 vs. 9.1 months; [3]). Another report demonstrated an improved OS when systemic relapse occurs >5 years from initial diagnosis compared to that of patients who had a systemic relapse <5 years or presented with de-novo metastatic disease [2]. Previous studies have documented prognostic factors in patients with de-novo metastasis, including age, race, estrogen receptor (ER) status, human epidermal receptor-2 (HER2) status, site of first metastases, and the number of sites of metastases [4–6]. Prior to 1996, the median OS for de-novo metastatic disease averaged about 2 years [6–18].

Over the past two decades, there have been many new treatment options shown to improve survival among patients with de-novo metastases, including newer endocrine therapies, HER2-targeted agents, and new chemotherapy combinations. Traditionally, surgery was utilized palliatively in metastatic breast cancer. However, several recent studies have suggested that surgery of the primary tumor may also have a role in improving survival [19–23]. This topic has been nicely reviewed recently, does not specifically deal with patients with de-novo metastasis, and will not be dealt with further in this manuscript [19].

We analyzed two cohorts of patients seen at breast cancer specific practices, compared the results to other reports and larger databases, and report our findings regarding the median OS of de-novo MBC.

Patients and methods

The records from a large breast oncology private practice and a second from the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database were retrospectively reviewed to identify patients with de-novo metastasis. Patients with de-novo metastatic disease included those patients diagnosed with proven metastases within 3 months of diagnosis of breast cancer. Excluded patients included: men, relapsed breast cancer, other malignancy, diagnosis before 1996 or after 2006, patients clinically and continuously disease-free after primary local regional therapy, one-time consultations, and patients primarily treated elsewhere. Patients diagnosed between 1996 and 2006 were chosen for our study population because they could benefit from the advances in multimodality breast cancer treatment over the past 20 years. This timeframe also ensured survival follow-up for at least 5 years.

At the time of diagnosis of de-novo metastasis, patients generally had a complete physical examination and ancillary labs that typically included complete blood count (CBC), complete metabolic panel (CMP), carcinoembryonic antigen (CEA), cancer antigen (CA) 15–3, bone scans with confirmatory bone radiographs, and computed tomography (CT) scans. Positron emission tomography (PET) scans, biopsies of metastatic sites when feasible, and magnetic resonance imaging (MRI) scans were performed when appropriate. Patients were restaged by imaging approximately every 3 months for the first year or as deemed appropriate by the treating physician, by whatever modality was adequate to follow disease. During the time period studied, treatment strategies for patients with hormone receptor-positive metastatic disease were conservative and hormonally oriented whenever possible. Cytotoxic chemotherapy generally was reserved for hepatic metastases, "visceral crisis," or for ER positive tumors that did not respond to at least one prior endocrine therapy. Patients with indolent and/or asymptomatic disease usually received endocrine therapy initially, and for as long as the disease remained responsive to estrogen blockade.

The literature search was performed using PubMed.gov using the search terms "breast cancer," "metastasis," "de-novo," and "survival." Studies included in our literature search were published between 1999 and 2014, had at least 50 patients, and included both retrospective and prospective cohorts. With permission, we compared our patient population and the UM/SCCC tumor database with other databases including the SEER program. A large body of data exists on surgery of the primary tumor in the setting of metastatic disease [9]. This literature was reviewed but not completely referenced in this paper. As another large-scale comparator for our series, in August 2014, we accessed median OS data from the National Cancer Data Base (NCDB). Subsequently, a recent letter from the Commission on Cancer (COC; 02/04/2015) requested that such data not be used for comparative purposes. However, since the data were acquired before the COC request, the NCDB data are referenced in this manuscript.

Statistical methods

We utilized the Kaplan–Meier product-limit method and the generalized Wilcoxon test to identify variables that were significantly associated with OS. In turn, prognostic factors that were flagged as significant individual predictors of OS were used (1) to construct a multivariate Cox proportional hazards regression model and (2) to generate adjusted z statistics and p values for each covariate. Finally, omnibus-likelihood ratio and Wald test statistics were generated to evaluate the overall fit of the model to the data. Data were manipulated and analyzed using the SPSS version 20 (SPSS Inc., Chicago, IL, USA) and R (R Core Team, Vienna, AT) statistical packages. The type I error (α) was set to 0.05 for all analyses, and each hypothesis test was assumed to be two-sided.

Table 1 Patient characteristics of a large breast cancer-specific private practice and the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database

Variable	Private practice ($n = 62$)		UM/SCCC ($n = 91$)	
	Number of patients	Valid percent	Number of patients	Valid percent
Age				
<50	21	19.6	25	27.5
>50	41	80.4	66	72.5
Ethnicity				
Non-Hispanic	41	80.4	55	60.4
Hispanic	10	19.6	36	39.6
Unknown	11	N/A	0	
ER				
Positive	45	73.8	55	72.4
Negative	16	26.2	21	27.6
Unknown	1	N/A	15	
HER2				
Positive	22	36.7	16	21.9
Negative	38	63.8	44	78.1
Unknown	2	N/A	31	
Subtype				
HR+/HER2+	18	30	11	18.6
HR+/HER2−	26	43.3	33	55.9
HR−/HER2+	4	6.7	4	6.8
HR−/HER2−	12	20	11	18.6
Unknown	2	N/A	32	
Dominant site				
Soft tissue	7	11.5	7	8.3
CNS	1	1.6	4	4.8
Bone	24	39.3	43	51.2
Visceral	29	47.5	30	35.7
Unknown	1	N/a	7	
Number of metastatic sites				
1	24	39.3	36	67.9
2	19	31.1	17	32.1
>2	18	29.5	Unknown	
Unknown	1	N/A	38	
Year of metastasis				
1996–2000	32	51.6	31	34.1
2001–2006	30	48.4	60	65.9
# of Lines of therapy (mean/median)				
Chemotherapy	3.8/3	Unknown		
Hormone therapy	1.7/1			
All	5.4/5			

ER estrogen receptor, *HER2* her-2-neu receptor, *CNS* central nervous system. valid percent: percentage excluding unknown patients

Results

Within the private practice, there were 62 patients and in the UM/SCCC tumor database, 91 patients that met our inclusion criteria. The basic patient demographics of our study population and that of the UM/SCCC tumor database appear in Table 1.

The primary endpoint of this study was to determine the median OS of de-novo metastatic breast cancer. The OS for the private practice was 41.0 months (46.0 for ER positive

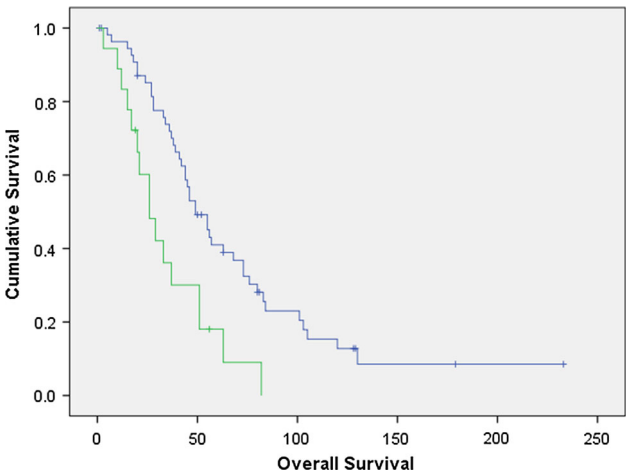

Fig. 1 Kaplan–Meier curve showing the significant improved overall survival among private practice patients whose tumors were found to be estrogen receptor positive, when compared to those that were estrogen receptor negative

and 26.0 for ER negative; Fig. 1) and 36.0 months for UM/SCCC (52 months for ER positive and 36 months for ER negative). One third of the patients in the UM/SCCC database ($n = 31$) had tumors with unknown HER2 status. ER negativity and site of dominant metastasis (visceral, CNS) were identified as being associated with a significantly worse prognosis within the private practice. Meanwhile, only the site of dominant metastasis (visceral, CNS) was associated with a significantly worse prognosis within the UM/SCCC database although there was a trend in favor of hormone receptor-positive patients. Age and ethnicity did not contribute significantly to the survival of patients within either cohort. A greater percentage of the UM/SCCC population (66 %) was diagnosed in the period from 2001 to 2006 than in the private practice (48 %).

We also explored the number of patients from the private practice and from the UM/SCCC tumor database that had lived for more than 10 years (Table 3). 7.6 % of the patients from the private practice and 2.2 % of the patients from UM/SCCC tumor database lived for >10 years, and as expected, were predominantly patients with ER positive tumors.

Discussion

Only since the 2000s has it been widely accepted that retrospective evaluation of MBC should separate de-novo metastases from systemically relapsed metastatic breast cancer. As mentioned earlier, previously treated breast cancer will likely be resistant to later therapies. This creates significant limitations with comparative survival data over time. Another issue is sensitivity of diagnostic testing. As imaging and laboratory technology improve, the detection of disseminated breast cancer occurs earlier. A patient with lower tumor burden or bone-only disease is more likely to have more durable responses to treatments, or be referred for metastasectomy or radiation. Patients with stage IV disease in older populations understandably would have a higher tumor burden than those with stage IV disease in recent papers. This further clouds interpretation of data spanning decades. Improvement over time could also, in part, be explained by better supportive care, such as the use of prophylactic (or reactionary) white blood cell growth factors or longer adherence to intended therapy due in part to more effective anti-emetics. Our retrospective study of patients with de-novo metastatic breast cancer among two breast cancer-specific practices revealed an OS of three or more years. This value is similar to other reports and databases documenting survival among this patient population during the late 1990's–early 2000's [24–30]. The 3 year median OS is approximately 1 year greater than data from earlier decades [6–18].

Although the majority of patients in the private practice had ER positive/HER2 negative tumors, many of the patients had prognostic variables that are normally associated with a relatively poor prognosis, such as number of metastatic sites and HER2 tumor status. However, only ER tumor status and site of dominant metastasis were found to hold prognostic weight among this patient population. Among the UM/SCCC tumor database, only the site of metastasis was shown to hold prognostic weight, although the trend in favor of ER + tumors mirrored that of the private practice patients and the data of Dawood et al. ([2]; Table 2). The median OS of the private practice and that of UM/SCCC were greater than older series. Compared with many of the older studies, both cohorts had the advantage of including those patients diagnosed in the late 1990's–early 2000's. Both cohorts of patients benefited from numerous breakthroughs in multimodality breast cancer treatment, including HER2-targeted therapy (trastuzumab), aromatase inhibitors (AIs), and the incorporation of taxanes with anthracyclines in breast cancer combination chemotherapy. Additionally, patients in both of our cohorts, similar to that of Dawood et al. [2] were generated within breast cancer-specific practices.

While Dawood et al. [2] present data suggesting that the survival for de-novo metastatic disease may be superior to that for recurrence, our data and literature review can neither confirm nor refute that claim. The median OS of our private practice group of 41 months, at first glance, appears superior to our recent publication for the same time frame (33 months; [32]) That study was limited to systemic recurrence only, thus eliminating the most favorable subgroup of patients (i.e., local–regional relapse and most of the soft tissue dominant patients). In addition, one recent paper focused on patients with HER2+ metastatic disease

Table 2 Results of a large breast cancer-specific private practice and the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database

Variable	Private practice			UM/SCCC			Dawood et al. (1992–2007)		SEER	
	Number of patients	OS	*p* value*	Number of patients	OS	*p* value*	Number of patients	OS	Number of patients	OS
All	62	41		91	36		643	39.2	17,752	20
Age										
<50	21	46	0.484	25	58	0.2	237	45.1	3,539	29
>50	41	37		66	30		393	38.1	14,213	17
Ethnicity										
Non-Hispanic	41	44	0.434	55	46	0.72	643	Unknown	16,271	19
Hispanic	10	37		36	33		0		1383	22
ER										
Positive	45	46	0.003	55	52	0.87	404	45.9	9,078	30
Negative	16	26		21	36		173	22.6	3,671	12
HER2										
Positive	22	41	0.82	16	55	0.66	130	41.4	Unknown	Unknown
Negative	38	39		44	36		397	42.7		
Dominant site										
Soft tissue	7	38	<0.0001	7	69	0.007	66	Unknown	Unknown	Unknown
CNS	1	5		4	29		6			
Bone	24	49		43	33		206			
Visceral	29	28		30	6		165			
Number of metastatic sites										
1	24	44	0.13	36	48	0.23	Unknown	Unknown	Unknown	Unknown
2	19	37		17	27					
>2	18	33		Unknown	–					

OS overall survival, *ER* estrogen receptor, *HER2* her-2-neu receptor, *CNS* central nervous system

* Log-rank

treated with first line trastuzumab-based therapy and broke down the patients into 3 subsets for comparison: de-novo metastases with surgical treatment of the primary lesion, de-novo metastases with no surgical treatment of the primary lesion, and recurrent disease [28]. Acknowledging the potential bias that referral for surgery introduces, they reported that OS was not better for patients with de-novo metastases than for those with recurrent disease: 37 and 40 months, respectively.

The differences between our two series and most others in Table 4 versus SEER and NCDB are striking. Of course, SEER patients were older, with 80 % >50 years of age (with most of those, more than 65 years at diagnosis), probably leading to greater mortality from comorbidities. In addition, our private practice series, although not specifically stated, was heavily weighted to a non-Hispanic Caucasian patient population. It has been widely published that African American patients (8.1 % in our series) have a worse prognosis, even when correcting for socioeconomic status [33, 34]. In the Dawood et al. paper [2], African American patients represented 12.1 % of the total population. In both that and our series, this is an underrepresented population, as the most recent US Cancer statistics from 2011 report an evenly matched age-adjusted breast cancer incidence rate for Caucasian (non-Hispanic) Americans and African Americans [35]. With regard to the NCDB, the Commission on Cancer has recently changed its guidelines for publicly reporting their survival rates. Our citation was accessed August 1st, 2014 antedating these new policies. It is remarkable how similar the SEER and NCDB survival statistics are for the time period in question and how markedly different they are from ours and other recent, smaller series. While differences in age distribution, ethnicity, comorbidities, and biologic factors (ER, PR, Her-

Table 3 Patients with an OS more than 10 years in a large breast cancer-specific practice and the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database

Database	Age at diagnosis	ER	HER2	Dominant metastatic site	Number of metastatic sites	Number of systemic therapies	OS (months)
Our series	30	Positive	Negative	Visceral	>2	6	120
UM/SCCC	37	Negative	Negative	Soft tissue	1	Unknown	122+
Our series	62	Positive	Unknown	Visceral	1	1	128+
Our series	60	Positive	Negative	Bone	>2	16	129+
Our series	72	Positive	Negative	Bone	2	18	130
UM/SCCC	66	Positive	Positive	Visceral	2	Unknown	155
Our series	57	Positive	Negative	Visceral	1	2	179+
Our series	47	Positive	Unknown	Visceral	2	7	233+

OS overall survival, *ER* estrogen receptor, *HER2* her-2-neu receptor

Table 4 Comparison of the overall survival seen in a large breast cancer-specific private practice and the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC) tumor database with that seen in the literature and in local and national databases

Source	Population (*n*)	Years	Median overall survival (months)
1970's–Early 1990's			
Slamon (2001) [15]	235	1995–1997	25.1
Friedel (2002) [10]	77	1960–1994	25.0
Andre (2004) [8]	343	1987–1993	23.0
Sledge (2003) [13]	229	1993–1995	22.2
Rahman (2000) [4]	1322	1973–1982	22.2
Pacini (2000) [18]	81	1991–1996	20.0
Esteban (1999) [17]	73	1987–1993	18.0
Brufman (1997) [14]	214	1989–1992	18.0
Aisner (1995) [16]	491	1982–1987	17.0
Dawood (2008) [6]	3796	1988–1993	15.0
Chia (2007) [11]	423	1991–1992	14.2
Zinser (1987) [12]	233	1973–1980	14.0
Late 1990's			
Private practice (2015)	62	1996–2006	41.0
UM/SCCC (2015)	91	1996–2006	36.0
Dawood (2010) [2]	643	1992–2007	39.0
Babiera (2006) [23]	224	1997–2002	32.1
Berghoff (2013) [25]	201	1999–2009	32.0
Guth (2014) [9]	92	1990–2009	32.0
Bertaunt (2015) [27]	236	1998–2009	29.2
Andre (2004) [8]	381	1994–2000	29.0
Gennari (2006) [26]	459	1998–2003	28.0
NCDB (2014) [31]	61,858	1996–2006	20.7
SEER (2015) [1]	17,752	1996–2006	20.0
2000's			
Yardley (2014) [30]	327	2003–2006	41.7
Infante (2009) [24]	61	2001–2005	40.8
Lobbezoo (2015) [3]	154	2007–2009	29.4

2 neu, and others) could lead to survival differences between series, the doubling of survival compared with SEER ad NCDB from our series and others [2, 24, 30] is so divergent that other explanations should be sought. It could be that patients in our series were better insured and therefore had greater access to care than many patients in

the SEER and NCDB series. The hypothesis we favor is that metastatic disease care rendered by a disease-specific multidisciplinary team provides better outcomes than expected than the larger, more inclusive, but less specialized series reported by SEER and NCDB. Specifically, in our two study cohorts, survival advantages with such specialized care teams likely could be due to earlier adoption of evidence-based best practices, knowledge of lesser known treatment alternatives, avoidance of potentially more harmful than beneficial interventions, and earlier access to novel agents through clinical trials. However, we also must consider that by excluding patients from our two cohorts who presumably chose to follow up with another oncologist or patients who did not have sufficient insurance to be seen at either center, we might have selected out patients with more adverse psychosocial or socioeconomic factors that predict poorer overall survival. Whatever the explanations might be for the differences between our and other contemporary series versus SEER and the NCDB, the authors laud the new NCDB survival tools application, which should, moving forward, help even the playing field between individual centers' statistics and the NCDB.

Conclusion

Our two series and other papers from the recent literature show that the median survival for patients with de-novo metastatic disease is in excess of 3 years compared with studies reported from prior to 1996. This is likely due to major advances in new palliative treatment options, while other explanations such as stage migration remain possible.

On the basis of our data and our literature review, we cannot confirm or refute contentions that survival for de-novo metastatic disease is better than for patients with recurrent disease. Our series, and others, confirm that a small, but real subset of these patients can have a prolonged survival with good quality of life in excess of 10 years.

Finally, and most importantly, ours and other recent small published series report a median survival that appears significantly better than larger national databases, such as SEER and NCDB. While there could be many alternative explanations, we hypothesize that ours and the other smaller series were reported by institutions with breast cancer-specific multidisciplinary teams versus the more comprehensive, but less specific, nature of the larger databases.

Compliance with Ethical Standards

Conflict of interest The authors declare there is no conflict of interest in the writing, preparing, or finalizing of this manuscript.

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