Original article

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Occult central nervous system involvement in patients with metastatic breast cancer: prevalence, predictive factors and impact on overall survival

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Background: As screening central nervous system (CNS) imaging is not routinely performed, the incidence and clinical relevance of occult CNS metastases in advanced breast cancer is unknown.

Patients and methods: All patients screened for participation in one of four clinical trials were included; each of the trials excluded patients with known CNS involvement and required screening CNS imaging. A cohort of breast cancer patients with symptomatic CNS metastases was identified from the IU Cancer Center Tumor Registry for comparison.

Results: From November 1998 to August 2001, 155 screening imaging studies were performed. Twenty-three patients (14.8%) had occult CNS metastases. HER-2 overexpression ($P = 0.02$) and number of metastatic sites ($P = 0.03$) were predictive of CNS involvement by multivariate analysis. Median survival from time of metastasis (1.78 versus 2.76 years; $P < 0.0001$) and from screening (4.67 versus 10.4 months; $P = 0.0013$) was shorter in patients with than without occult CNS metastasis. Survival among patients with occult CNS metastasis was similar to patients with symptomatic CNS disease.

Conclusions: Patients with CNS involvement, whether occult or symptomatic, have an impaired survival. Occult CNS metastasis is relatively common, but impact on survival of treating occult CNS disease in patients with progressive systemic metastases is questionable.

Key words: breast cancer, central nervous system, metastasis, natural history

Introduction

Clinically evident central nervous system (CNS) metastases are expected in about 10–15% of patients with metastatic breast cancer. Survival after the identification of symptomatic CNS metastases is generally short with a median survival of ~4 months; 2-year survival is <2% [1, 2]. Younger age, single metastasis, surgical resection, whole brain radiation therapy and chemotherapy have been associated with prolonged survival in multivariate analyses. Despite the poor prognosis associated with symptomatic CNS metastasis, most patients ultimately die of systemic disease progression [3].

Autopsy series, generally completed before the advent of effective systemic therapies, report a much higher incidence of CNS metastasis (Table 1). As routine CNS imaging is not recommended for asymptomatic patients and autopsy rates have declined dramatically [4], the incidence of clinically occult CNS disease in patients with metastatic breast cancer receiving modern systemic therapy is unknown. Similarly, the clinical relevance of occult CNS metastasis, survival after identification of occult CNS disease and the importance of CNS therapy are unknown.

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As angiogenesis is required for local growth and dissemination of breast cancer, inhibition of angiogenesis offers an attractive therapeutic target. Although expected to have minimal toxicity, early clinical trials identified bleeding at previously unrecognized CNS metastases [5] as a potential serious complication of anti-angiogenic therapy. To ensure patient safety, most subsequent trials excluded patients with any CNS involvement. The requirement for CNS imaging as a criterion for enrollment in trials of novel antiangiogenic agents provides a unique opportunity to investigate the prevalence and clinical relevance of occult CNS metastasis in patients with advanced breast cancer.

Patients and methods

All patients screened for participation in one of four clinical trials evaluating novel antiangiogenic agents at Indiana University or Memorial Sloan Kettering Cancer Center were included in the analysis (Table 2). Each of the trials excluded patients with known CNS involvement and required either head computed tomography (CT) scan or brain magnetic resonance imaging (MRI) prior to enrollment. Local institutional review boards approved all protocols; patients provided informed consent prior to CNS imaging. Demographics, disease characteristics, treatment history and survival were abstracted from the medical record; the referring oncologist confirmed survival when needed. A consecutive cohort of breast cancer patients with symptomatic CNS metastasis treated at Indiana University from 1996 to 2001 was identified for survival

Table 1. Incidence of central nervous system (CNS) metastasis in breast cancer based on autopsy series

Series	Period	No. of patients	CNS metastasis	Comments
Lesse [19]	1938–47	71	24%	
Abrams [20]	1943–47	167	28.8%	CNS examined in 45 patients
Aronson [15]	1953–62	204	25%	Greater incidence in younger patients
Viadana [21]	1956–67	374	20% age <50 years	
			12% age ≥50 years	
Cifuentes [22]	1959–74	707	31%	18% brain parenchyma
Tsukada [6]	1959–79	1044	30%	18% unrecognized
				Greater incidence in younger patients
				Lower survival (50.6 versus 61.0 months)
Amer [7]	1962–76	368	36%	20% unrecognized
				Greater incidence if adjuvant therapy
				Lower survival (15.8 versus 20.5 months)
de la Monte [16]	1965–83	187	35–65%	Greater incidence in younger patients
Cho [23]	1966–75	141	26%	CNS examined in 122 patients
Posner [24]	1970–76	98	17%	
Lamovec [25]	1972–89	261	18.2%	Survival ≤2 months
Hagemeister [8]	1973–77	133	30%	14% unrecognized

Table 2. Trials contributing patients to analysis

	AVF776g	AVF2119g	ME-001	ME-002
Antiangiogenic agent	rhuMAb VEGF	rhuMAb VEGF	2ME2	2ME2
Study design				
Phase	II	III	I	I
Treatment	rhuMAb VEGF monotherapy	capecitabine ± rhuMAb VEGF	2ME2 monotherapy	docetaxel + 2ME2
ECOG PS	0 or 1	0 or 1	0 or 1[a]	0 or 1
Prior chemotherapy	>1 required	anthracycline and taxane required	>1 required	0–1 only
Screening period	Nov. 1998–Apr. 2000	Dec. 2000–Dec. 2001	Mar. 2000–Oct. 2001	Sept. 2000–Aug. 2001

[a]Karnofsky performance status ≥80.

ECOG PS, Eastern Cooperative Oncology Group performance status; rhuMAb VEGF, recombinant humanized monoclonal antibody to vascular endothelial growth factor; 2ME2, 2-methoxyestradiol.

comparisons. As details of prior systemic therapy, steroid receptor status and HER-2 overexpression were not routinely available, symptomatic patients were not included in the analysis of predictive factors.

Logistic regression was used to identify predictive factors for occult CNS involvement. CNS metastasis (present versus not present) was considered a binary response variable. An initial univariate analysis was conducted to screen for potential predictive factors; all factors reaching significance at the 0.15 level were included in the multivariate model. Wald chi-square tests and odds ratios along with corresponding 95% confidence intervals were calculated. Three different survival intervals were analyzed: survival from initial diagnosis of breast cancer, survival from first distant metastasis and survival from on-study screening CNS imaging. Survival curves were constructed according to the method of Kaplan and Meier. Log-rank tests were employed to compare survival among the three patient cohorts (screened, no CNS metastasis; screened, occult CNS metastasis; symptomatic CNS metastasis).

Results

From November 1998 to August 2001, 155 screening imaging studies were performed; 11 patients were screened twice. Median age at diagnosis was 42.7 (range 26–76) years. Median time from first metastasis to screening was 12 months. Patients had received a median of three prior chemotherapies (range 0–13). Twenty-three patients (14.8%) had occult CNS metastases (Table 3). Identification of occult CNS metastases by CT (12 of 86 patients) and

Table 3. Patient characteristics

	Screening cohort		Symptomatic cohort (n = 73)
	No CNS metastasis (n = 132)	Occult CNS metastasis (n = 23)	
Median age, years (range)	43.5 (26–76)	41.0 (28–55)	48 (30–73)
ECOG PS			
0	54 (41%)	2 (9%)	NA
1	78 (59%)	21 (91%)	
Prior chemotherapy regimens[a]	3 (1–13)	3 (0–6)	NA
Sites of disease[b]	2 (1–5)	3 (1–4)	2 (1–4)
ER-positive	66 of 132 (50%)	10 of 22 (45%)	29 of 51 (59%)
HER-2-positive[c]	26 of 104 (20%)	9 of 20 (45%)	10 of 20 (50%)
Trial			
AVF776g	39	8	–
AVF2119g	46	8	–
ME-001	32	7	–
ME-002	15	0	–

[a]Includes neoadjuvant, adjuvant or overt metastatic chemotherapy.
[b]Sites of disease treated as a continuous variable.
[c]Patients were considered HER-2-positive if 3+ overexpression by immunohistochemistry or gene amplification by fluorescence *in situ* hybridization.
ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; NA, not available.

MRI (11 of 69 patients) was similar. Screening identified single parenchymal lesions in nine patients; 12 patients had multiple lesions. Isolated leptomeningeal or dural involvement was found in two patients. Seventy-three consecutive patients with symptomatic CNS metastasis referred for radiation therapy from 1996 to 2001 comprised the symptomatic cohort. Screened patients were slightly younger, likely representing bias in referral for clinical trials.

Univariate analysis identified the number of sites of metastatic disease, performance status and HER-2 overexpression (HER-2-positive includes 3+ by immunohistochemistry or gene amplification by fluorescence *in situ* hybridization) as predictors of CNS metastasis (Table 4). HER-2 overexpression (P = 0.02) and number of metastatic sites (P = 0.03) remained predictive of CNS involvement by multivariate analysis; age (P = 0.052) and performance status (P = 0.054) were of borderline predictive value. Among asymptomatic patients undergoing screening CNS imaging, survival, whether from time of initial diagnosis, first metastasis or on-study CNS screening, was shorter for patients with compared to without occult CNS involvement (Figure 1 and Table 5). Lead- or length-time bias did not explain these differences as the initial disease-free interval (18.5 versus 22.2 months) and time from first distant metastasis to CNS screening (11.4 versus 12.1 months) was similar in patients with and without occult CNS involvement. Survival for patients with CNS involvement was similar, whether diagnosed clinically (symptomatic) or on screening images (occult).

Twenty-one patients with occult CNS metastases received whole-brain radiation therapy; two patients with small solitary CNS lesions and rapidly progressive systemic disease received no CNS therapy. Twenty-one patients with occult CNS metastasis have died, all from apparent systemic disease progression. No patient with occult CNS disease developed neurological symptoms (focal deficits, seizures or need for chronic corticosteroids). Seven patients without apparent CNS involvement at screening subsequently developed symptomatic CNS disease requiring radiotherapy. Radiotherapy provided effective palliation of neurological symptoms in all six patients for whom details are available; all six succumbed to systemic disease. We were not able to determine how many patients presenting with symptomatic CNS metastasis died of systemic disease versus CNS progression.

Discussion

We found occult CNS metastasis in ~15% of patients with disseminated breast cancer screened for participation in antiangiogenic clinical trials. The patients we screened were young, heavily pretreated and highly selected, limiting the ability to generalize our results to the wider population of patients with metastatic disease. Nonetheless, the incidence in our series is consistent with previously reported, unselected autopsy series. Tsukada et al. found clinically unrecognized CNS involvement in 18% of 1044 breast cancer patients at autopsy [6]. Similar rates of occult CNS disease

Table 4. Predictors of occult central nervous system metastasis

	Odds ratio	*P* value
Univariate		
Sites of metastatic disease[a]	2.14 (1.29–3.52)	0.002
ECOG PS (1 or 0)	6.20 (1.38–27.82)	0.017
HER-2 (positive or negative)	3.28 (1.23–8.72)	0.018
Age at diagnosis, years	0.95 (0.90–1.10)	0.11
ER	0.83 (0.34–2.06)	0.81
Prior chemotherapy regimens[b]	0.87 (0.65–1.18)	0.38
Disease-free interval	0.98 (0.96–1.00)	0.18
Duration of metastatic disease	1.00 (0.99–1.02)	0.45
Specific sites of metastasis		
Bone	1.97 (0.81–4.82)	0.17
Lung	2.43 (0.97–6.14)	0.07
Liver	0.71 (0.27–1.84)	0.64
LN/ST	1.31 (0.53–3.25)	0.65
Skin	2.59 (1.03–6.50)	0.06
Scan type (MRI versus CT)	1.28 (0.50–3.29)	0.61
Multivariate		
Sites of metastatic disease[a]	1.90 (1.09–3.28)	0.03
Age at diagnosis, years	0.94 (0.88–1.00)	0.052
ECOG PS (1 or 0)	4.83 (0.99–23.46)	0.054
HER-2 (positive or negative)	3.58 (1.22–10.55)	0.02

[a]Sites of disease treated as a continuous variable.
[b]Includes neoadjuvant, adjuvant or overt metastatic chemotherapy.
CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; LN/ST, lymph node or soft tissue; MRI, magnetic resonance imaging.

were reported by Amer [7] and Hagemeister et al. [8]. Given the prevalence of occult CNS involvement, clinical trials employing therapy known or suspected to exacerbate problems associated with CNS metastasis (such as an increased risk of bleeding or seizure) should consider mandatory screening.

Amer first suggested that systemic therapy may alter the natural history of breast cancer, leading to an increase in CNS metastasis [7]. Although adjuvant therapy increased overall survival, patients who relapsed after adjuvant therapy had a higher incidence of CNS metastasis in one series [9]. More recently, Carey et al. reported an excellent disease-free survival but disproportionate CNS relapse after aggressive neoadjuvant therapy [10]. An increase in CNS relapse after initial chemotherapy for metastatic disease has also been suggested. Thirty per cent of patients treated with epirubicin and docetaxel combination therapy subsequently developed symptomatic CNS metastasis [11]. A similar frequency of CNS metastasis was found after initial response to paclitaxel; 12% of patients had isolated CNS relapse with continued control of systemic disease [12].

Two explanations have been offered for the apparent increase in CNS metastasis after chemotherapy: first, the effectiveness of the blood–brain barrier and secondly, prolonged survival of patients after initial recurrence allows microscopic CNS metastasis to become clinically evident. Our data cannot fully address this question as most patients in our study were heavily pretreated before CNS imaging. Muss et al. used early CT technology to image 116 patients with disseminated breast cancer. CNS lesions were found in 11 of 37 (30%) patients with CNS symptoms but only 1 of 79 (2%) patients without CNS symptoms [13]. The increased prevalence of occult CNS metastasis in our patients likely represents both improvement in imaging technology and patient selection; the impact of differential exposure to systemic therapy is not clear. However, the consistency between the frequency of occult CNS metastasis in our patients and historical autopsy series suggests the impact of chemotherapy may be modest rather than large.

We were able to identify several factors associated with an increased risk of occult CNS metastasis. Performance status and number of extracranial sites of disease likely reflect bulk of systemic disease rather than tumor biology. The association of HER-2 overexpression and CNS metastasis deserves further investigation. Crivellari et al. retrospectively measured HER-2 expression in patients developing symptomatic CNS disease after initial chemotherapy [11]. Although overexpression (3+ by immunohistochemistry) was found in 10 of 16 (62%) patients, HER-2 was not assessed in patients without CNS metastasis, thereby limiting conclusions. An increase in CNS involvement has also been reported in patients receiving trastuzumab [14]. Prior autopsy studies found an inverse correlation between patient age and CNS metastasis [6, 15, 16]. Age was not predictive of occult CNS disease in our analysis, likely due to the young age of patients attracted to early-phase clinical trials. Although other authors have debated the relative sensitivity of contrasted CT and brain MRI for detection of CNS metastasis [17, 18], both appeared equally effective as screening modalities in our patients.

Initial disease-free interval was similar for patients with and without CNS involvement but patients with CNS metastasis had an impaired survival. Somewhat surprisingly, the survival of patients with occult CNS disease was identical to that of patients with symptomatic CNS lesions, whether measured from initial diagnosis, first recurrence or diagnosis of CNS metastasis. The median survival after diagnosis of occult CNS metastasis in our patients is similar to that reported for patients with symptomatic lesions in other series as well [1, 10]. These results imply a unique and aggressive biology of tumors trophic for the CNS with symptoms dependent on the anatomic location of the lesions. Given the disparity in survival, stratification for CNS involvement in phase III trials is warranted if patients with CNS metastasis are enrolled.

The impact of identifying and immediately treating occult CNS metastasis in our patients was questionable at best. End-of-life details are known for 21 of 23 patients with occult CNS lesions; all died of systemic disease progression without intervening CNS symptoms. Occult CNS metastasis appeared to be a marker for, rather than a cause of, limited survival. We cannot exclude the possibility that some patients were spared development of CNS symptoms as nearly all received whole-brain radiation therapy after diagnosis of occult CNS disease. Although some authors have raised the question of prophylactic CNS radiation in high-risk patients as a strategy to improve survival [11], we cannot

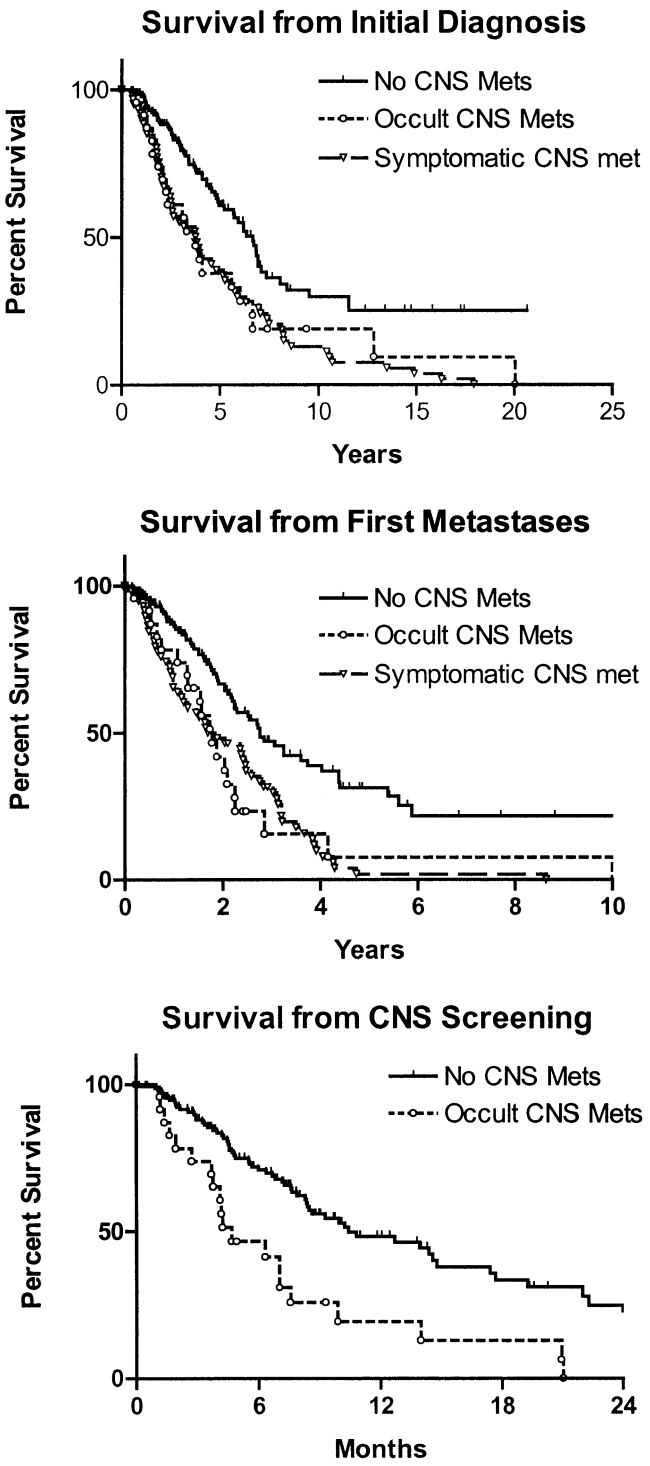

Figure 1. Survival comparisons. (**A**, **B**) Impaired survival in patients with central nervous system (CNS) metastasis, whether occult or symptomatic. (**C**) Survival from time of CNS screening is shorter in patients with occult CNS metastasis (4.67 versus 10.43 months; $P = 0.0013$).

recommend either routine CNS screening or prophylactic therapy in patients with uncontrolled systemic disease. However, our results cannot be generalized to patients with less advanced disease. Might patients with HER-2-positive breast cancer with prolonged disease control with trastuzumab benefit from CNS screening? This increasingly important clinical question remains unanswered and deserves further study.

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Table 5. Survival based on central nervous system (CNS) involvement

Survival from	Asymptomatic cohort		Symptomatic cohort (n = 73)
	No CNS metastasis (n = 132)	Occult CNS metastasis (n = 23)	
Diagnosis (years)	6.68	3.75	3.76
First metastasis (years)	2.76	1.78	1.84
CNS screening (months)	10.4	4.67	(10.4)[a]

[a]Survival from identification of symptomatic CNS metastasis.

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