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ORIGINAL PAPER

Long-term survival with metastatic cancer to the brain

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Metastatic cancer to the brain has a poor prognosis. The focus of this work was to determine the incidence of long-term ($\geq$2 y) survival for patients with brain metastases from different primary cancers and to identify prognostic variables associated with prolonged survival. A retrospective review of 740 patients with brain metastases treated over a 20 y period identified 51 that survived 2 or more years from the time of diagnosis of the brain metastasis. Prognostic variables that were examined included age, sex, histology, tumor number and location, and treatment. In the 51 patients, 35 (69%) had single lesions and 16 (31%) had multiple tumors. For all tumor types (740 patients), the actuarial survival rate was 8.1% at 2 y, 4.8% at 3 y, and 2.4% at 5 y. At 2 y, patients with ovarian carcinoma had the highest survival rate (23.9%) and patients with small cell lung cancer (SCLC) had the lowest survival rate (1.7%). At 5 y, survival rates were 7.8% for ovarian carcinoma, 2.9% for non-SCLC, 2.3% for melanoma and renal cell carcinoma, 1.3% for breast carcinoma and there were no survivors with SCLC, gastrointestinal, bladder, unknown primary, or prostate cancer. Age, sex, histology, location for single tumors, systemic chemotherapy, and stereotactic radiosurgery did not significantly influence survival. The presence of a single lesion ($P=0.001$, chi-square test), surgical resection ($P=0.001$), and WBRT ($P=0.009$) were favorable prognostic variables for extended survival. Multiple bilateral metastases was a poor prognostic indicator ($P=0.001$). Multivariate analysis showed younger age ($P<0.05$), single metastasis ($P<0.0001$), surgical resection ($P<0.0001$), whole brain radiation therapy ($P<0.0001$), and chemotherapy ($P=0.0288$) were associated with prolonged survival. 29 patients (57%) died of systemic disease progression, 9 (18%) died of central nervous system progression, and the cause of death was unknown in 3 (6%). Patients with a single non-SCLC, breast, melanoma, renal cell, and ovarian carcinoma brain metastasis have the best chance for long-term survival if treated with surgical resection and WBRT. *Medical Oncology* (2000) **17**, 279–286.

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Introduction

Metastatic cancer to the brain carries a poor prognosis with a median survival of one month without treatment. These patients usually die as a result of their brain tumor.[1,2] Treatment with corticosteroids has been

shown to extend median survival to two months and whole brain radiation therapy (WBRT) will prolong median survival to three to six months.[1,3] Those patients treated with WBRT usually die from their progressive systemic cancer and not from their brain metastases.[2] For patients with a single brain metastasis, surgical resection followed by WBRT was associated with a statistically significant increase in survival from 15 weeks to 40 weeks and from 6 months to 10 months in two randomized series, respectively.[4,5] The efficacy of surgery for patients with multiple brain metastases has not been established.[1,2,6,7]

Some reports have focused on the length of survival from the time of diagnosis of the primary disease while others have addressed extended survival after the development of brain metastases.[8–11] Specific tumor histologies that have previously been associated with long-term survival from the time of diagnosis have included non-small cell lung cancer (NSCLC), renal cell carcinoma, and breast carcinoma.[8–13] Few patients survive beyond two years after the development of metastatic cancer to the brain. We performed a retrospective analysis of those patients with brain metastases treated at our institution over a 20 y period and identified those patients surviving more than two years after their presentation with an intracranial tumor. For each individual tumor type, we determined the actuarial incidence of survival at 2, 3, and 5 y. Specific variables that included age, sex, tumor histology, number of metastases, location of metastases, surgical resection, WBRT, systemic chemotherapy, and stereotactic radiosurgery (SRS) were examined to determine whether any variable was associated with prolonged survival.

Patients and methods

Patient population

A retrospective review of medical records identified 740 patients (355 men, 385 women) with brain metastases treated at the University of Minnesota Hospital and Clinic (UMHC) from 1973 to 1993. Follow-up was available for all patients from the time they developed brain metastases up to 5 y. From this group of 740 patients, 51 survived for 2 or more years. In all cases, the presence of a brain metastasis was confirmed by computed tomography (CT) of the head, magnetic resonance (MR) imaging, or the pathological examination of tissue obtained by either stereotactic brain biopsy or open surgical resection. Patients in the early part of the series were evaluated using a prototype CT scanner. Patients with carcinomatous meningitis were excluded from the study.

For each patient, we recorded age, sex, histological type of the primary tumor, time from initial diagnosis to presentation with brain metastases, number of brain metastases, intracranial location of brain metastases, treatment of the brain metastases, length of survival after the development of brain metastases, and cause of death. The cause of death was either due to widespread systemic disease, extensive central nervous system (CNS) disease, or could not be determined from the hospital chart. The criteria for determining whether the cause of death was due to either systemic disease or CNS disease was based on the radiologic results of the patient's last staging studies and their physical examination at the last recorded clinic visit. Some patients died more than 5 y after the development of brain metastases and the exact cause of death could not be determined because of the presence of both extensive CNS and systemic disease. Extent of systemic disease was analyzed only to determine whether it was the cause of death since patients with disseminated cancer usually died from multi-system failure. The neurologic cause of death was usually lethargy progressing to coma with eventual herniation and cardiorespiratory arrest. The incidence of long-term survivors for each specific tumor type was determined using the entire patient cohort. There is no regional bias to specific tumor histologies with the exception of hematologic malignancies at UMHC.

Statistical analysis

The actuarial survival at 2, 3, and 5 y was calculated according to the methods of Kaplan–Meier.[14] If patients were alive at last follow-up they were treated as censored data. We compared the 51 long-term survivors to those patients that did not survive 2 y to determine whether there was any significant difference between the proportions of patients with certain characteristics or the treatments received by the two groups. The statistical testing was performed using the chi-square test or Fischer's exact test where applicable for small numbers. The following variables were analyzed: age, sex, primary tumor type, tumor location if single, tumor location if multiple, presence of a

single metastasis, presence of multiple unilateral metastases, presence of multiple bilateral metastases, and treatment received after the development of brain metastases. The treatment modalities which were analyzed included surgical resection, WBRT, systemic chemotherapy, and SRS. The difference between the mean age of the two groups was assessed using Student's *t*-test. Multivariable analysis using Cox's proportional hazard model was performed for the entire patient cohort to identify variables associated with prolonged survival. The variables chosen for the multivariate analysis were those analyzed on univariate analysis. Significance level was set at $P < 0.05$. All statistical tests were performed using the SAS (Statistical Analysis Systems, Raleigh, NC) program.

Treatment philosophy

Patients with well-controlled systemic disease and a single, surgically accessible brain metastasis were treated with resection and WBRT. Patients with advanced systemic disease or multiple brain metastases usually received WBRT alone. In select cases, patients with multiple metastases had one individual lesion causing significant neurological compromise surgically resected prior to WBRT. Patients that did not receive WBRT were felt to be either too ill because of the extent of their intracranial and/or systemic disease or they refused the treatment. Patients that received systemic chemotherapy were felt to have measurable systemic disease where the response to therapy could be measured and they were able to tolerate the treatment. More recently, patients with stable systemic disease and a surgically inaccessible brain metastasis received both SRS and WBRT for their intracranial disease.

Results

Characteristics and treatment for long-term survivors

The demographic and treatment data for the 51 long-term survivors with either single or multiple metastases are listed in Table 1. Miscellaneous primary tumors included one patient (2%) each who had prostate carcinoma, lymphoma, Wilms' tumor, bladder carcinoma, and gastrointestinal carcinoma. The duration from the time of diagnosis of systemic cancer to the development of brain metastases varied widely. All patients with an unknown primary cancer presented with neurological signs and symptoms. The mean time to presentation with brain metastases was 9 months for NSCLC, 53 months for breast carcinoma, 13 months for renal carcinoma, 37 months for melanoma, 27 months for ovarian carcinoma, 3 months for SCLC, and 11 months for sarcoma.

In the long-term survivors, 22 patients (43%) with single metastases were treated with surgical resection followed by WBRT. 12 patients (24%) with single metastases had WBRT alone and 1 patient (2%) had surgery without WBRT. 6 of 16 patients (12%) with multiple brain metastases received WBRT alone. 3 patients (6%) had surgery for a single symptomatic metastasis followed by WBRT and 1 patient (2%) had a biopsy before receiving WBRT. 4 patients with multiple tumors (8%) had surgery for a single metastasis prior to WBRT and were later treated with SRS for progressive intracranial disease. 1 patient (2%) had both WBRT and SRS and 1 patient (2%) received no treatment.

Survival

The Kaplan–Meyer survival curve for the 740 patients that developed brain metastases is shown in Figure 1. Table 2 demonstrates the actuarial 2, 3, and 5 y survival of the patients with different primary tumors. The actuarial incidence of long-term survival for each specific tumor type was determined in the 740 patients and is outlined in Table 3. For the entire cohort, the actuarial incidence of survival was 8.1% at 2 y, 4.8% at 3 y, and 2.4% at 5 y. 51 patients survived 2 or more years from the time they developed intracranial disease (Figure 2). 32 patients were alive at 3 y and 10 patients were alive at follow-up of more than 5 y. There were no 3 y survivors for SCLC and gastrointestinal cancer or 5 y survivors for bladder carcinoma, unknown primary carcinoma, or prostate carcinoma.

10 patients (20%) lived for more than 5 y, 6 (12%) with single metastases and 4 (8%) with multiple metastases. 9 (18%) patients died from progressive CNS disease; 4 (8%) with a single lesion and 5 (10%) with multiple tumors. Progression of the systemic disease was the cause of death in 29 patients (57%) of which 23 (45%) had a single brain metastasis and 6 (12%) had multiple tumors. In 3 patients (6%), the cause of death could not be determined from the medical record.

Table 1 Characteristics of long-term survivors with metastatic cancer to the brain

	No. of Metastases		
Characteristic	*Single no. (%)*	*Multiple no. (%)*	*Total no. (%)*
No. of patients	35 (69%)	16 (31%)	51(100%)
Sex			
male	15 (29%)	8 (16%)	23 (45%)
female	20 (39%)	8 (16%)	28 (55%)
Primary tumor type			
NSCLC	9 (18%)	2 (4%)	11 (22%)
SCLC	0 (0%)	2 (4%)	2 (4%)
breast carcinoma	6 (12%)	3 (6%)	9 (18%)
renal cell carcinoma	6 (12%)	1 (2%)	7 (14%)
melanoma	3 (6%)	4 (8%)	7 (14%)
ovarian carcinoma	2 (4%)	1 (2%)	3 (6%)
unknown	2 (4%)	3 (6%)	5 (10%)
sarcoma	2 (4%)	0 (0%)	2 (4%)
miscellaneous[a]	5 (10%)	0 (0%)	5 (10%)
Tumor location			
right			39 (48%)
frontal	5 (6%)	2 (2%)	7 (9%)
temporal	1 (1%)	2 (2%)	3 (4%)
parietal	3 (4%)	3 (4%)	6 (7%)
occipital	4 (5%)	6 (7%)	10 (12%)
cerebellum	2 (2%)	9 (11%)	11 (13%)
hypothalamus		1 (1%)	1 (1%)
thalamus		1 (1%)	1 (1%)
left			39 (48%)
frontal	8 (10%)	5 (6%)	13 (16%)
temporal	1 (1%)	2 (2%)	3 (3%)
parietal	1 (1%)	3 (4%)	4 (5%)
occipital	7 (9%)	6 (7%)	13 (16%)
cerebellum	3 (4%)	3 (4%)	6 (7%)
midline			4 (5%)
vermis		3 (4%)	3 (4%)
corpus callosum		1 (1%)	1 (1%)
Treatment			
surgery	1 (2%)		1 (2%)
surgery + WBRT	22 (43%)	3 (6%)	25 (49%)
biopsy + WBRT		1 (2%)	1 (2%)
WBRT	12 (24%)	6 (12%)	18 (35%)
WBRT + SRS		1 (2%)	1 (2%)
surgery + WBRT + SRS		4 (8%)	4 (8%)
none		1 (2%)	1 (2%)
Cause of death			
alive	6 (12%)	4 (8%)	10 (20%)
CNS	4 (8%)	5 (10%)	9 (18%)
systemic	23 (45%)	6 (12%)	29 (57%)
unknown	2 (4%)	1 (2%)	3 (6%)

SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer; WBRT: whole brain radiation therapy; SRS: stereotactic radiosurgery; CNS: central nervous system.
[a]Miscellaneous tumors were lymphoma, Wilms' tumor, gastrointestinal, prostate, and bladder carcinomas.

Prognostic variables

When we compared the 51 long-term survivors to those patients that had died by 2 y, we found that the presence of a single metastasis was found to be associated with extended survival ($P = 0.001$) and the presence of multiple bilateral metastases was a poor prognostic variable ($P = 0.001$) on the univariate analysis. Univariate analysis also revealed that surgical resection

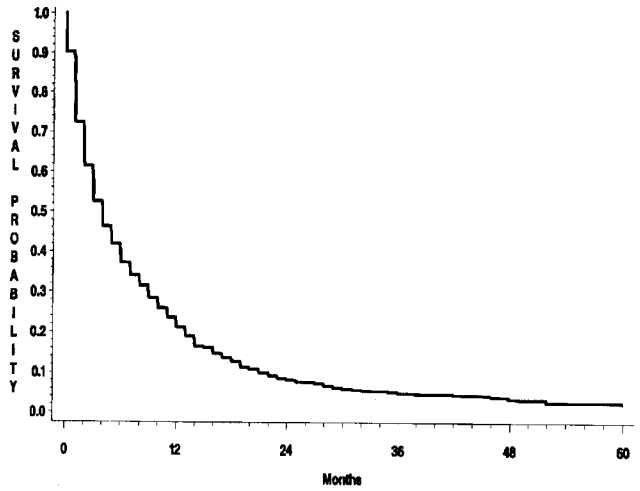

Figure 1 *Kaplan–Meier 5 y survival curve for 740 patients with metastatic cancer to the brain.*

Table 2 Actuarial survival with metastatic cancer to the brain

		Duration		
Histology	*No.(%)*	*2 y*	*3 y*	*5 y*
All tumors	740	8.1%	4.8%	2.4%
NSCLC	183 (24.7)	7.9%	5.0%	2.9%
Breast carcinoma	121 (16.4)	8.0%	6.9%	1.3%
SCLC	110 (14.9)	1.7%	0%	0%
Melanoma	82 (11.1)	9.0%	4.5%	2.3%
Renal cell carcinoma	49 (6.6)	21.7%	12.4%	2.3%
GI cancer	45 (6.1)	2.3%	0%	0%
Unknown primary	34 (4.6)	12.3%	6.6%	0%
Bladder carcinoma	14 (1.9)	11.5%	5.8%	0%
Ovarian carcinoma	13 (1.8)	23.9%	7.8%	7.8%
Prostate carcinoma	10 (1.3)	13.3%	13.3%	0%

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; GI: gastrointestinal.

($P = 0.001$) and whole brain radiation therapy ($P = 0.009$) were associated with prolonged survival. Systemic chemotherapy ($P = 0.21$) and stereotactic radiosurgery ($P = 0.06$) did not significantly extend survival. Table 3 demonstrates all the variables tested in the analysis. Multivariate analysis showed younger age ($P < 0.05$), single metastasis ($P < 0.0001$), surgical resection ($P < 0.0001$), whole brain radiation therapy ($P < 0.0001$), and chemotherapy ($P = 0.0288$) were associated with prolonged survival (Table 4).

Discussion

The most appropriate treatment for brain metastases remains controversial as new therapies such as SRS become increasingly utilized. Surgical resection of single accessible lesions or a single symptomatic lesion in the patient with multiple brain metastases is an accepted neurosurgical practice, provided the systemic disease is stable. Two prospective randomized trials have demonstrated the benefit of resection in patients with a single brain metastasis.[4,5] In one of these studies, regardless of the state of their system-ic disease, patients with a single brain metastasis who had resection and WBRT compared to WBRT alone, survived longer, had less frequent local recurrences, and had improved quality of life.[4] An early review of 13 patients with NSCLC who survived more than 5 y after craniotomy revealed that excision of the single metastatic lesion with or without WBRT provided the best chance for long-term survival.[11] In our series, surgical resection and WBRT for patients with single brain metastases was associated with significant long-term survival.[1] Surgical resection of multiple brain metastases is not universally accepted by neurosurgeons.

In some studies, SRS extended survival in patients with 1 or 2 brain metastases.[1,15,16] The use of SRS for 3 or 4 lesions appears to be no more effective than WBRT alone.[16] In our patients, SRS with either WBRT alone or surgery and WBRT did not significantly influence survival. Reasons that SRS did not prolong survival to a statistically significant degree may be due to the small number of treated patients or its exclusive use in patients with multiple lesions. Adjuvant chemotherapy has been reported to be the most independent predictor of disease-free survival in patients with NSCLC and a solitary brain metastasis.[17] Adjuvant chemotherapy with surgical resection and WBRT was found to significantly influence survival and improve quality of life in 50 patients with single or multiple NSCLC brain metastases.[12] In our study, multivarate analysis found chemotherapy along with single metastasis, surgical resection, WBRT, and younger age were associated with prolonged survival.

Prognostic variables that have been reported to be associated with prolonged survival in patients with brain metastases include inactive or absent extracranial disease, age younger than 60 y, female sex, breast carcinoma histology, treatment with chemotherapy after diagnosis of brain metastasis, two or fewer brain metastases, Karnofsky performance status of 70 or higher, the presence of neurological symptoms for more than 4 weeks prior to diagnosis, complete

Table 3 Variables that influenced long-term survival with metastatic cancer to the brain

	No. of survivors (%)		
Variable	*≥ 2 y (n = 51)*	*< 2 y (n = 689)*	*P*[a]
Age (mean)	57.6 y	52.9 y	NS (0.121)[c]
Sex (male/female)	23/28 (45/55)	330/359 (48/52)	NS (0.866)
Primary tumor type			
breast carcinoma	9 (18)	112 (16)	NS (0.795)
NSCLC	11 (22)	172 (25)	NS (0.391)
SCLC	4 (8)	106 (15)	NS (0.059)
melanoma	7 (14)	75 (11)	NS (0.533)
prostate carcinoma	1 (2)	9 (1)	NS (0.513)[b]
ovarian carcinoma	3 (6)	10 (1)	NS (0.054)[b]
renal cell carcinoma	7 (14)	42 (6)	NS (0.070)
GI carcinoma	1 (2)	44 (6)	NS (0.356)
lymphoma	1 (2)	10 (1)	NS (0.055)[b]
unknown carcinoma	5 (10)	29 (4)	NS (0.077)[b]
bladder carcinoma	1 (2)	13 (2)	NS (1.000)[b]
miscellaneous[d]	S3 (6)	16 (2)	NS (0.137)[b]
Tumor location			
single	35	360	
frontal	13 (37)	124 (34)	NS (0.448)
temporal	2 (6)	81 (23)	NS (0.115)[b]
parietal	11 (31)	32 (1)	NS (0.706)[b]
occipital	4 (12)	37 (1)	NS (0.788)[b]
cerebellum	5 (14)	67 (19)	NS (0.761)
multiple	16	329	
cerebrum	8 (50)	236 (72)	NS (0.473)[b]
cerebrum	1 (6)	2 (1)	NS (1.000)[b]
cerebrum and cerebellum	7 (44)	86 (26)	NS (0.303)[b]
cerebrum and brain stem	0 (0)	2 (1)	NS (1.000)[b]
brain stem	0 (0)	3 (1)	NS (1.000)[b]
No. of tumors			
single	35 (69)	352 (51)	0.001
multiple unilateral	5 (10)	98 (14)	NS (0.202)[b]
multiple bilateral	11 (21)	239 (35)	0.001
Treatment			
surgery	29 (57)	160 (23)	0.001
WBRT	50 (98)	583 (85)	0.009
chemotherapy	13 (25)	127 (18)	NS (0.212)
SRS	4 (8)	18 (3)	NS (0.058)[b]

NSCLC: non-small cell lung cancer; SCLC: small cell lung cancer; GI: gastrointestinal. NS: not significant: WBRT: whole brain radiation therapy; SRS: stereotactic radiosurgery.
[a]Chi-square test, except where indicated by b or c.
[b]Fischer's exact test.
[c]Student's *t*-test.
[d]Miscellaneous tumors were Wilms' tumor and sarcoma.

resection of a primary lung tumor, interval between resection of the primary tumor and a single brain metastasis, interval from the diagnosis of systemic cancer to brain metastases, and interval from the treatment of the intracranial disease to its recurrence.[15,17–20] Factors associated with short survival after surgical resection include the presence of disseminated disease, poor neurological performance status, detection of the brain metastasis within a year of diagnosing the primary cancer, increasing age, male gender, and infratentorial tumor location.[15] We did not find sex, tumor histology, single tumor location in the brain, or the presence of multiple unilateral tumors within the brain to influence survival. The presence of a single meta-

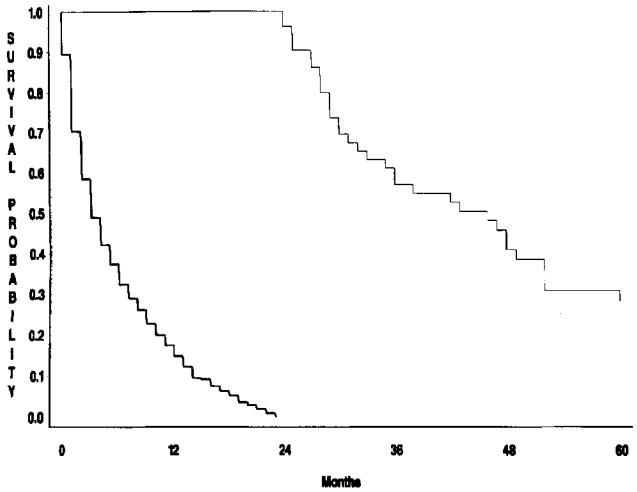

Figure 2 *Kaplan–Meier 5 y survival curves for the long-term survivors (thin line; n = 51) compared to those patients that expired within 2 y (bold line; n = 689).*

Table 4 Multivariate analysis for 740 patients with brain metastases

Variable	*P*[a]	*RR*[b]
Surgery	0.0001	0.472
WBRT	0.0001	0.467
Chemotherapy	0.0288	0.780
Age	0.0487	1.006
Sex	0.5712	1.048
Tumor location		
frontal	0.0823	0.760
temporal	0.7783	1.067
parietal	0.0246	0.679
occipital	0.6310	1.106
cerebellum	0.0775	0.183
cerebrum	0.0837	0.210
cerebrum and cerebellum	0.0929	0.217
brain stem	0.3768	0.356
Multiple *vs* single lesions	0.0001	0.450

[a]Cox's proportional hazard model.
[b]RR: relative risk.

stasis was a favorable prognostic variable for extended survival in contrast to having multiple bilateral tumors which were associated with a poor prognosis.

The actuarial survival after the development of metastatic cancer to the brain has not been well documented and few series have followed patients for more than 2 y. For patients with NSCLC brain metastases treated with surgery, the 2 y survival rate ranges from 0–78%, with an average survival of 28%.[21] One series reported a 5 y survival rate of 12.5% for NSCLC.[18,20] As of 1991, there were 16 patients with metastatic NSCLC to the brain that were reported disease-free at 10 y.[10] In a series of 231 patients with NSCLC brain metastases, Wronski *et al.* found that women survived significantly longer than men, patients with single metastatic lesions survived longer than those with multiple metastases, patients with a high Karnofsky performance score before surgery had prolonged survival, and patients with supratentorial tumors survived longer than those with cerebellar lesions.[20] Postoperative WBRT has been suggested to reduce local failure rates after surgery for NSCLC brain metastases.[22] Our actuarial survival for NSCLC at 2 y was 7.9%, with a 5 y survival rate of 2.9%.

Patients with melanoma brain metastases have an average 2 y survival rate of 16% with a range of 0–25%.[21] We found survival rates of 9.0% at 2 y and 2.3% at 5 y for patients with melanoma. Breast cancer metastatic to the brain has an 18% (range 0–33%) survival rate at 2 y with the 5 y survival rate ranging from 0–17%.[18,21] In a small series of 8 patients with a single breast cancer brain metastasis treated with surgical resection and WBRT, there was a 5 y survival rate of 38% compared to 1 of 8 patients with NSCLC and 0 of 14 patients with unknown primary tumors.[13] In that same study, whole brain irradiation alone for patients with breast cancer brain metastases resulted in a 3 y survival rate of 33% with no 5 y survivors.[13] Our survival rate for metastatic breast cancer was 8.0% at 2 y and 1.3% at 5 y. Brain metastases from renal cell carcinoma has an average 2 y survival rate of 35% with a range of 0–70%.[21] 5 y survival rates for renal cell carcinoma range from 0–8.5%.[18] We found a 2 y survival rate for ovarian carcinoma of 23.9% with a 5 y survival rate of 7.8%. The 2 y survival rate for gastrointestinal cancer was 0% in our patients, although one report had a 5.5% rate for colorectal carcinoma.[18] In one report, the 2 y survival rate for patients with unknown primary carcinoma was 19% compared to 6.6% for our patients.[10] The small number of patients in each specific tumor type precluded reaching statistical significance for prolonged survival, even though there was a trend toward extended survival with some tumor types such as ovarian carcinoma.

The cause of death in patients with brain metastases is most commonly due to systemic disease progression, neurologic causes, or both processes. In one study of patients with brain metastases from NSCLC, one-third of patients died from neurologic causes, one-third from

systemic disease, and one-third from a combination of both.[20] Boogerd *et al* found in 137 breast cancer patients with brain metastases that 19% survived for more than 1 y and neurologic disease progression was the cause of death in 68%.[19] According to Salvati *et al*, the cause of death was usually systemic disease progression in patients with a solitary brain metastasis where the primary malignancy was diagnosed during life.[10] In a report of 122 patients with surgically resectable single brain metastases treated with linear accelerator stereotactic radiosurgery, the rate of CNS progression resulting in death was 25%.[23]

In conclusion, approximately 70% of patients with brain metastases who survived for more than 2 y had single lesions. The actuarial survival rates at 2, 3, and 5 y were 8.1%, 4.8%, and 2.4%, respectively. Patients with ovarian carcinoma, NSCLC, melanoma, renal cell carcinoma, and breast carcinoma had the highest survival rates at 5 y. Sex, histology, location of single tumors, and SRS did not influence survival and the presence of multiple bilateral metastases was a poor prognostic indicator on univariate analysis. On multivariate analysis, younger age, single metastasis, surgical resection, whole brain radiation therapy, and chemotherapy were associated with prolonged survival. Systemic disease progression was the most common cause of death. Surgical resection of single lesions combined with WBRT appears to offer the best chance for prolonged survival for those histologies listed above.

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