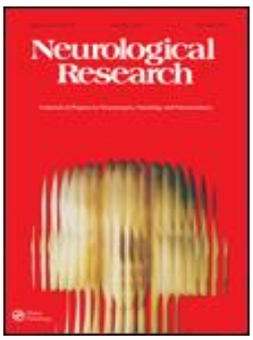

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Patients undergoing surgery of intracranial metastases have different outcomes based on their primary pathology

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Patients undergoing surgery of intracranial metastases have different outcomes based on their primary pathology

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Objectives: Patients with a variety of different primary cancers can develop intracranial metastases. Patients who develop intracranial metastases are often grouped into the same study population, and therefore an understanding of outcomes for patients with different primary cancers remain unclear.
Methods: Adults who underwent intracranial metastatic tumor surgery from 1997–2011 at a single institution were retrospectively reviewed. Primary pathologies were compared using Fisher's exact and Student's *t*-test, and Cox regression analysis was used to identify factors associated with survival.
Results: About 708 patients underwent surgery during the reviewed period, where 269 (38%) had non-small cell lung cancer (NSCLC), 106 (15%) breast cancer (BC), 72 (10%) gastrointestinal (GI) cancers, 88 (12%) renal cell cancer (RCC), and 88 (12%) melanoma. The most notable differences were that NSCLC patients were older, BC younger, BC had more primary tumor control, and NSCLC less extracranial spread. BC had longer survival, RCC had longer local progression free survival (PFS), and NSCLC had longer distal PFS. The factors independently associated with survival for NSCLC (female, recursive partitioning analysis (RPA) class, primary tumor control, solitary metastasis, tumor size, adenocarcinoma, radiation, discharge to home), BC (age, no skull base involvement, radiation), GI cancer (age, RPA class, Karnofsky performance scale (KPS), lack of preoperative motor deficit, non-esophageal tumors, non-hemorrhagic tumors, avoidance of new deficits), melanoma (preoperative seizures, solitary metastasis, smaller tumor size, discharge to home, chemotherapy), and RCC (KPS, chemotherapy) were distinctly different.
Discussion: These differences between patients with different primary cancers support the fact that patients with intracranial disease are not all the same and should be studied by their primary pathology.

Keywords: Breast, Gastrointestinal, Lung, Melanoma, Metastatic brain tumor, Recurrence, Renal, Surgery, Survival

Introduction

Metastatic brain cancer is the most common type of intracranial tumor in adults.[1,2] It is estimated that there will be 100 000 to 180 000 new cases diagnosed in the United States each year.[1,2] The most common primary sources include lung, breast, melanoma, renal cell (RCC), and gastrointestinal (GI) cancers.[1,2] These primary cancers have varying degrees of sensitivity to radiation, dissimilar systemic disease burden, different chemotherapeutic regimens, and, most importantly, disparate prognoses.[1,2] Despite these dissimilarities, these histologically different tumors are grouped into the same study population when they metastasize to the brain and require brain surgery.[3–9] This grouping may be potentially erroneous, and hinder progress in understanding and developing optimal treatment for patients with different primary cancers.

Studies on metastatic brain cancer separated by primary pathology are few and limited.[10–13] This limitation has made it difficult to understand survival prognoses and recurrence profiles for patients with different primary cancers. A better understanding may translate into more optimal treatment regimens, once these cancers metastasize to the brain, guided by primary pathology and not metastatic site. As a result, the goals of this study were to: (1) understand differences in pre, peri, and postoperative

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characteristics between patients with different primary cancers that metastasize to the brain, and (2) ascertain factors independently associated with survival for each of these primary pathologies.

Methods

Patient selection

Institutional Review Board approval was first obtained prior to initiating this study (36875). All adult patients (age $>$ 18 years) who underwent intracranial surgery (resection or biopsy) for an intracranial metastasis (single or multiple) at a single, tertiary care institution between 1997 and 2011 were tabulated and reviewed. The pathology was determined by a senior neuro-pathologist in all cases.

Recorded variables

Seven hundred and eight patients underwent surgery for a single or multiple intracranial metastases during the reviewed period. The clinical, operative, and hospital course records of these patients were retrospectively reviewed. The information collected from clinical notes included patient demographics, comorbidities, presenting symptoms, neurological function, radiographic imaging findings, and use of adjuvant therapy. Patients were assigned a preoperative Karnofsky performance scale (KPS) by a reviewer blinded to patient outcomes at the clinical visit prior to surgery during a chart review.[14] The presence of a motor deficit was defined as any decrease in strength, and a language deficit as any combination of receptive and/or expressive aphasia. A cognitive deficit was any complaint of decreased mental status or ability, and a vision deficit was defined as any decrease in visual acuity or field perception. Patients were also assigned a recursive partitioning analysis (RPA) classification group as previously defined.[15]

All MRI images were obtained and reviewed. The characteristics that were recorded included the lesion's size (largest diameter based on gadolinium enhancement), specific lobe involvement, and number of intracranial metastases. Extent of resection was classified as gross-total resection (GTR), near total resection (NTR), and sub-total resection (STR) if there was no enhancement, a rim of enhancement, and residual nodular enhancement in the resection cavity on postoperative MRI, respectively.[16] In addition to brain MRIs, patients generally underwent computed tomography scans of the chest, abdomen, pelvis, and spine with and without contrast or positron emission tomography scans before surgery to identify metastatic body sites.

Outcome definitions

The primary outcomes that were evaluated for each primary cancer were overall survival, local recurrence, and distal recurrence. Survival data was obtained from the social security index database. Time to death was defined as the time from cranial surgery to death, where patients whose deaths were unconfirmed were classified as lost to follow-up at the time of their last clinic visit. Local recurrence was defined as the recurrence or progression of tumor in the previous surgical cavity. Distal recurrence was defined as presence of new tumor in the brain not adjacent to the previous surgical cavity. Time to local or distal recurrence was defined as the time from surgery to MRI diagnosis of recurrence. Patients whose recurrence was unconfirmed were classified as lost to follow-up at the time of their last neuro-imaging.

General treatment strategy

In general, surgical resection was pursued when patients presented with intracranial metastases causing symptoms or at risk of causing symptoms either from location or swelling. Patients typically had at least 3 months of expected survival. Biopsy was pursued when only diagnosis was desired and/or for patients who presented with poor survival prognoses. The general goal of surgical resection was to achieve GTR of the tumor without causing new iatrogenic deficits. Surgery was pursued for multiple metastases when the metastases were easily accessible and/or causing symptoms.

Postoperative MRI with gadolinium was typically performed at 3-month intervals following surgery, or when new or exacerbating symptoms occurred. The use of adjuvant therapy, including whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and chemotherapy, were determined by a multi-disciplinary team (neurosurgery, neuro-oncology, medical oncology, and radiation oncology) as well as the patients and their families.

Statistical analysis

Patients were grouped by their histology, where each group consisted of $>$ 50 patients. This number was assigned *a priori* in order to have sufficient numbers to perform multivariate analyses. Groups with less than fifty patients were excluded from the analyses.

Summary data were presented as mean $\pm$ standard deviation for parametric data and as median [interquartile range (IQR)] for non-parametric data. The student's *t*-test and Fisher's exact test were used to make inter-group comparison for continuous and categorical data, respectively. Stepwise multivariate proportional hazards regression analyses were performed for each type of primary cancer to identify factors independently associated with survival, local recurrence, and distal recurrence. In these analyses, univariate analysis was first performed to identify potential associations between radiographic, preoperative, operative, perioperative, and pathologic variables with survival. All variables associated with

survival in univariate analysis ($P < 0.10$) were then included in a step-wise multivariate proportional hazards regression model. For continuous variables, the variables were dichotomized to identify the greatest statistical association. Overall survival, local progression free survival (PFS), and distal PFS as a function of time were plotted using the Kaplan–Meier method. Log-rank analyses were used to compare Kaplan–Meier plots between each primary cancer (GraphPad Prism 5, La Jolla, CA, USA). Values with $P < 0.05$ in these analyses were considered statistically significant. JMP 9 (SAS, Cary, NC, USA) was used unless otherwise specified.

Results

Patient population and histological groups

A total of 708 patients underwent surgery for a single or multiple intracranial metastases during the reviewed period (Table 1). Of these 708 patients, 269 (38%) had non-small cell lung cancer (NSCLC), 106 (15%) had breast cancer (BC), 72 (10%) had GI cancers, 88 (12%) had RCC, and 122 (17%) had other primary cancers. Among NSCLC patients, 214 (80%) had documented pathological data, where 163 (76%) had adenocarcinoma and 51 (24%) had squamous cell carcinoma. Among GI cancer patients, 35 (49%) had colon cancer, 11 (15%) had pancreatic/bile duct cancer, 8 (11%) had esophageal cancers, 8 (11%) had stomach cancer, 4 (6%) had liver cancer, and 6 (8%) had salivary cancers. Among the 122 patients with other primary cancers, 34 (28%) had small cell lung cancer, 17 (14%) had primary bone cancers, 12 (10%) had bladder cancer, 10 (8%) had ovarian/testicular cancer, 9 (7%) had hematopoietic cancers, 10 (8%) had thyroid cancer, 9 (7%) had endometrial cancer, 8 (7%) had prostate cancer, 10 (8%) had unknown primary cancer, and 3 (2%) had vaginal/cervical cancer. These patients with other cancers were excluded from further analyses by histology.

Table 1 Preoperative characteristics of patients undergoing surgery of intracranial metastases separated by primary cancer (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC). The bolded values are statistically different than one or more of the other histological groups ($P < 0.05$)

Study Population ($n = 708$)						
	NSCLC	Breast	GI	Melanoma	RCC	All
	$n = 269$	$n = 106$	$n = 72$	$n = 88$	$n = 51$	$n = 708$
Characteristics	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Demographics						
Age*	**60.5 ± 10**	**53.2 ± 12**	57.6 ± 14	58.3 ± 12	60.9 ± 12	58.4 ± 12
Male	149 (55%)	**1 (0.9%)**	38 (53%)	55 (63%)	35 (69%)	336 (47%)
KPS**	80 (70–80)	80 (70–80)	80 (70–90)	80 (70–90)	80 (70–80)	80 (70–80)
Headaches	103 (38%)	**55 (52%)**	28 (39%)	34 (39%)	16 (31%)	293 (41%)
Seizures	50 (19%)	18 (17%)	7 (10%)	11 (13%)	8 (16%)	110 (16%)
Motor deficit	100 (37%)	39 (37%)	33 (46%)	**16 (18%)**	20 (39%)	254 (36%)
Language deficit	45 (17%)	11 (10%)	12 (17%)	17 (19%)	8 (16%)	111 (16%)
Cognitive deficit	57 (21%)	13 (12%)	17 (24%)	**23 (26%)**	10 (20%)	146 (21%)
Vision deficit	36 (13%)	**25 (24%)**	14 (19%)	17 (19%)	9 (18%)	120 (17%)
Tumor characteristics						
Control of primary tumor	196 (73%)	**85 (80%)**	50 (69%)	58 (66%)	41 (80%)	502 (71%)
Extracranial spread	**77 (29%)**	66 (62%)	45 (63%)	46 (52%)	35 (69%)	324 (46%)
No. of body met sites**	**1 (1–2)**	**1 (1–3)**	2 (1–3)	**2 (1–3)**	2 (1–3)	1 (1–3)
RPA Class						
RPA Class 1	**70 (26%)**	22 (21%)	13 (18%)	17 (19%)	6 (12%)	152 (21%)
RPA Class 2	**143 (53%)**	67 (63%)	43 (60%)	56 (64%)	38 (75%)	421 (59%)
RPA Class 3	56 (21%)	17 (16%)	16 (22%)	15 (17%)	7 (14%)	135 (19%)
Solitary metastasis	182 (68%)	**56 (53%)**	45 (63%)	52 (59%)	37 (73%)	460 (65%)
Radiographics						
Tumor size*	3.0 ± 1.4	3.3 ± 1.3	3.4 ± 1.2	2.9 ± 1.3	2.7 ± 1.1	3.2 ± 1.5
Location						
Frontal lobe	102 (38%)	37 (35%)	16 (22%)	34 (39%)	21 (41%)	256 (36%)
Temporal lobe	30 (11%)	15 (14%)	12 (17%)	18 (20%)	5 (10%)	102 (14%)
Parietal lobe	62 (23%)	25 (24%)	14 (19%)	20 (23%)	8 (16%)	154 (22%)
Occipital lobe	40 (15%)	10 (9%)	13 (18%)	18 (20%)	11 (22%)	101 (14%)
Cerebellum	55 (20%)	26 (25%)	20 (28%)	8 (9%)	10 (20%)	140 (20%)
Brainstem	2 (0.7%)	3 (3%)	2 (3%)	2 (2%)	0 (0%)	12 (2%)
Skull base	11 (4%)	4 (4%)	2 (3%)	0 (0%)	1 (2%)	25 (4%)
Bone involvement	12 (4%)	5 (5%)	5 (7%)	2 (2%)	2 (4%)	41 (6%)
No. of brain mets**	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–3)	1 (1–1)	1 (1–2)
Hemorrhagic	37 (14%)	10 (9%)	13 (18%)	38 (43%)	19 (37%)	138 (19%)

*mean ± standard deviation, ** median (interquartile range); KPS = Karnofsky performance score; RPA = recursive partitioning analysis

Preoperative characteristics and differences between histological groups

The preoperative characteristics are summarized in Table 1. The average ± standard deviation age of the entire cohort was 58.4 ± 12 years. The preoperative RPA classes of the patients were RPA 1 in 152 (21%), RPA 2 in 421 (59%), and RPA 3 in 135 (19%). Radiographically, 460 (65%) presented with solitary metastasis, and the median [IQR] number of intracranial metastases was 1 [1,2].

Among the histological groups, NSCLC patients were older than patients with BC ($P = 0.0001$) and GI cancer ($P = 0.04$). Patients with BC were younger than patients with GI ($P = 0.02$), melanoma ($P = 0.005$), and RCC ($P = 0.0003$). Male patients were less commonly seen with BC than other cancers ($P = 0.0001$). With regards to symptoms, headaches were more common in BC than NSCLC ($P = 0.02$) and RCC ($P = 0.02$). Patients with melanoma less commonly had motor deficits than patients with NSCLC ($P = 0.001$), BC ($P = 0.006$), and GI cancers ($P = 0.0003$). Likewise, cognitive deficits were more common in melanoma than BC ($P = 0.02$), and vision deficits in BC than NSCLC ($P = 0.02$).

Primary tumor control was more common in breast cancer patients than melanoma ($P = 0.03$). NSCLC patients less commonly had extracranial spread than patients with BC ($P = 0.0001$), GI ($P = 0.0001$), melanoma ($P = 0.0001$), and RCC ($P = 0.0001$). NSCLC patients had on average less metastatic sites than patients with BC ($P = 0.0001$), GI ($P = 0.0001$), melanoma ($P = 0.0001$), and RCC ($P = 0.0001$). With regards to RPA class, NSCLC were more commonly RPA Class 1 than RCC ($P = 0.03$). Solitary metastasis was less common in BC than patients with NSCLC ($P = 0.009$) and RCC ($P = 0.02$).

Radiographically, the average size of a melanoma metastasis was smaller than BC ($P = 0.04$) and GI cancer ($P = 0.02$). RCC metastases were also smaller than breast ($P = 0.008$) and GI cancer ($P = 0.004$). Patients with melanoma less commonly had cerebellar metastases than NSCLC ($P = 0.01$), breast ($P = 0.007$), and GI cancers ($P = 0.003$). BC had less intracranial metastases than patients with NSCLC ($P = 0.01$) and RCC ($P = 0.05$). Melanoma patients presented with more intracranial metastases than NSCLC ($P = 0.03$) and GI cancers ($P = 0.04$). Hemorrhagic tumors were more common in melanoma patients than NSCLC ($P = 0.0001$), BC ($P = 0.0001$), and GI cancers ($P = 0.0007$). RCC were more commonly hemorrhagic than NSCLC ($P = 0.0002$), breast ($P = 0.0001$), and GI cancers ($P = 0.01$).

Perioperative characteristics and differences between histological groups

The perioperative outcomes are summarized in Table 2. GTR, NTR, and STR were achieved in 502 (71%), 126 (18%), and 59 (8%) patients. Biopsy was pursued in 21 (3%) patients. About 80 (11%) patients underwent surgery for multiple metastatic tumors. Following surgery, 65 (9%) had a new motor deficit, 20 (3%) had a language deficit, and 16 (2%) had a new vision deficit. At last follow-up, 13 (2%) incurred a wound infection, 10 (1%) an intracranial hemorrhage requiring re-operation, 29 (4%) deep vein thrombosis (DVT)/pulmonary embolism (PE), and 9 (1%) pneumonia.

Postoperative characteristics and differences between histological groups

The postoperative outcomes are summarized in Table 2. Five hundred and fourteen (73%) patients died at last follow-up, where the median survival was 9.3 months. The 6, 12, and 18-month survival rates were 60.7%, 41.5%, and 31.0%, respectively (Fig. 1). About 107 (15%) had local recurrence at the site of the surgical cavity, where the 6, 12, and 18-month local PFS was 93.3%, 84.3%, and 77.7%, respectively (Fig. 2). A total of 226 (32%) had distal intracranial recurrence following surgery, where the 6, 12, and 18-month distal PFS was 71.7%, 54.6%, and 47.0%, respectively (Fig. 3).

Leptomeningeal disease was more common following BC resection than NSCLC ($P = 0.005$), GI ($P = 0.005$), and RCC ($P = 0.002$). BC patients more commonly received chemotherapy than patients with NSCLC ($P = 0.002$), GI ($P = 0.01$), and RCC ($P = 0.03$). RCC patients less commonly received brain radiation therapy than NSCLC ($P = 0.03$), breast ($P = 0.004$), and melanoma ($P = 0.003$). RCC patients less commonly underwent WBRT than NSCLC ($P = 0.03$), BC ($P = 0.004$), and melanoma ($P = 0.03$).

The median survival (Fig. 1A) was longest for patients with NSCLC as compared to patients with BC ($P < 0.0001$), GI ($P < 0.0001$), melanoma ($P < 0.0001$), and RCC ($P < 0.0001$). Likewise, patients with BC had longer median survival than patients with GI ($P = 0.005$) and RCC ($P = 0.04$). The local PFS rate (Fig. 2) was longer in RCC patients than patients with NSCLC ($P = 0.02$), BC ($P = 0.004$), and GI cancer ($P = 0.02$). Distal recurrence occurred less frequently for NSCLC than BC ($P = 0.02$) and melanoma ($P = 0.002$). The distal PFS rates (Fig. 3) were longer for patients with NSCLC than BC ($P = 0.03$) and melanoma ($P = 0.002$).

Factors independently associated with overall survival by histological groups

The results are summarized in more detail in Table 3 and Fig. 1. For patients with NSCLC, the factors that remained independently associated with prolonged survival were: female gender, RPA Class 1, control of primary cancer, solitary brain metastasis, tumor size > 2 cm, adenocarcinoma pathology, discharge to home,

and postoperative brain radiation. For patients with BC, the factors that remained independently associated with prolonged survival were: age < 65 years, no skull base involvement, and postoperative brain radiation. For patients with GI cancer, the factors that remained independently associated with prolonged survival were: age < 75 years, RPA Class < 3, KPS > 50, lack of motor deficit, non-esophagus primary, non-hemorrhagic tumors, and avoidance of language deficit. For patients with melanoma, the factors that remained independently associated with prolonged survival were: seizures, solitary metastasis, tumor size < 2 cm, discharge to home, and postoperative chemotherapy. For patients with RCC, the factors that remained independently associated with prolonged survival were: KPS > 60 and postoperative chemotherapy. When including all patients, the factors that remained independently associated with prolonged survival for patients with any type of primary cancer were: female gender, RPA Class 1, lack of motor deficit, lack of cognitive deficit, solitary brain metastasis, tumor size < 2 cm, discharge to home, postoperative chemotherapy, and postoperative brain radiation.

Discussion

Prior studies on metastatic brain tumors separated by histology

Patients who develop intracranial metastases are generally considered to have dismal prognoses regardless of the extent of their systemic disease.[1,2] Studies on patients with intracranial metastases often combine patients with different primary cancers into the same study population.[3–9,17] This grouping of all patients intuitively appears to be flawed. This is because patients with different types of primary cancers have varying degrees of disease burden, undergo different treatment regimens, receive dissimilar systemic therapies, and have different median survival times.[1,2] Moreover, these studies will be biased by the primary cancers that comprise the

Table 2 Peri and postoperative characteristics of patients undergoing surgery of intracranial metastases separated by histology (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC). The bolded values are statistically different than one or more of the other histological groups ($P < 0.05$)

Study Population ($n = 708$)

	NSCLC	Breast	GI	Melanoma	RCC	All
	$n = 269$	$n = 106$	$n = 72$	$n = 88$	$n = 51$	$n = 708$
Characteristics	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Surgery						
Gross-total resection	198 (74%)	73 (69%)	53 (74%)	62 (70%)	40 (78%)	502 (71%)
Near-total resection	42 (16%)	20 (19%)	14 (19%)	14 (16%)	9 (18%)	126 (18%)
Sub-total resection	23 (9%)	8 (8%)	4 (6%)	10 (11%)	2 (4%)	59 (8%)
Biopsy	6 (2%)	5 (5%)	1 (1%)	2 (2%)	0 (0%)	21 (3%)
En bloc resection	18 (7%)	10 (9%)	7 (10%)	6 (7%)	8 (16%)	60 (8%)
Cortical mapping	9 (3%)	5 (5%)	1 (1%)	0 (0%)	3 (6%)	21 (3%)
Multiple mets resected	29 (11%)	18 (17%)	7 (10%)	12 (14%)	4 (8%)	80 (11%)
New symptoms						
Motor deficit	19 (7%)	10 (9%)	8 (11%)	9 (10%)	7 (14%)	65 (9%)
Language deficit	4 (1%)	3 (3%)	3 (4%)	5 (6%)	2 (4%)	20 (3%)
Vision deficit	5 (2%)	7 (7%)	2 (3%)	2 (2%)	0 (0%)	16 (2%)
Adjuvant therapy						
Chemotherapy	90 (33%)	**54 (51%)**	23 (32%)	35 (40%)	16 (31%)	249 (35%)
Radiation therapy	174 (65%)	76 (72%)	45 (63%)	64 (73%)	**24 (47%)**	449 (63%)
Whole brain XRT	131 (49%)	60 (57%)	33 (46%)	45 (51%)	**16 (31%)**	340 (48%)
Stereotactic XRT	91 (34%)	37 (35%)	19 (26%)	32 (36%)	17 (33%)	222 (31%)
Clinical trials	18 (7%)	8 (8%)	8 (11%)	11 (13%)	7 (14%)	60 (8%)
Complications						
Wound infection	5 (2%)	2 (2%)	3 (4%)	1 (1%)	1 (2%)	13 (2%)
Intracranial hemorrhage	5 (2%)	1 (0.9%)	1 (1%)	1 (1%)	1 (2%)	10 (1%)
Leptomeningeal disease	17 (6%)	**17 (16%)**	2 (3%)	8 (9%)	0 (0%)	51 (7%)
DVT/PE	10 (4%)	2 (2%)	6 (8%)	3 (3%)	3 (6%)	29 (4%)
Pneumonia	2 (0.7%)	1 (0.9%)	0 (0%)	1 (1%)	0 (0%)	9 (1%)
Survival						
Deaths	189 (70%)	68 (64%)	57 (79%)	70 (80%)	39 (76%)	514 (73%)
Median survival	**37.1**	**13.1**	6.3	6.9	11.5	9.3
Local recurrence	45 (17%)	22 (21%)	10 (14%)	11 (13%)	2 (4%)	107 (15%)
12-month local PFS rate	74.1%	72.5%	70.9%	83.5%	**100%**	84.3%
Distal recurrence	73 (27%)	**41 (39%)**	23 (32%)	**39 (44%)**	20 (39%)	226 (32%)
12-month distal PFS rate	**63.0%**	**48.1%**	39.4%	36.5%	63.1%	54.6%

*mean ± standard deviation, ** median (interquartile range); DVT = deep vein thrombosis; PE = pulmonary embolism; XRT = radiation therapy.

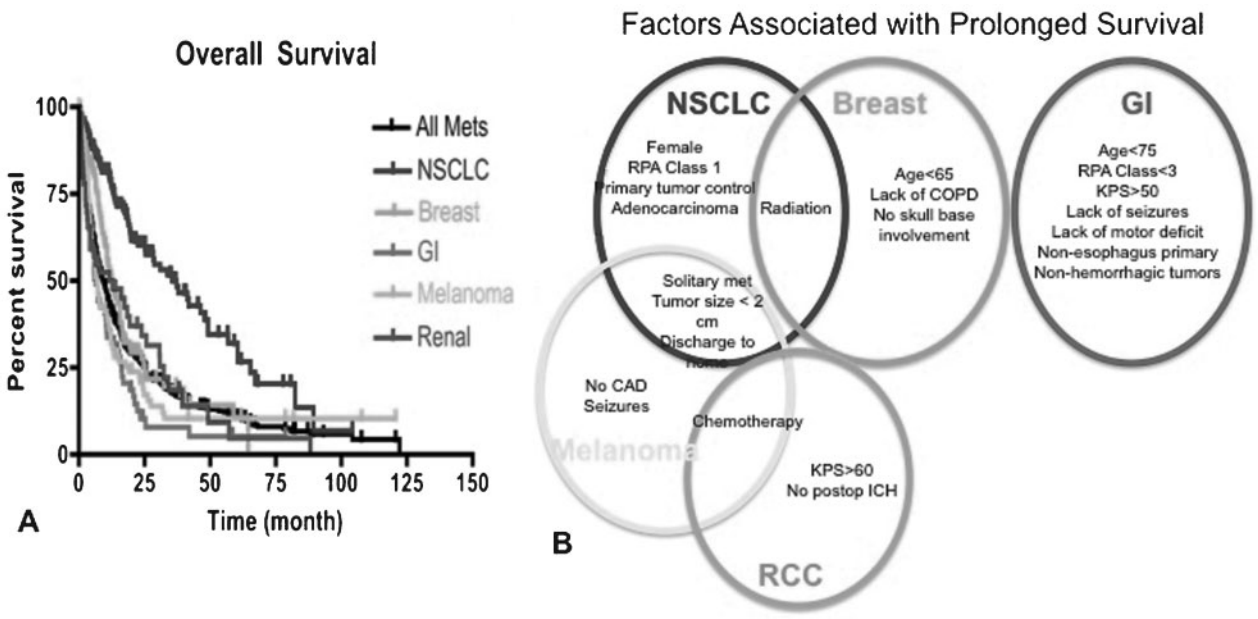

Figure 1 Overall survival for patients with different primary cancers. (A) Kaplan–Meier survival curves for patients separated by histology (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC). The median survival for all patients was 9.3 months, while the median survival was 37.1 months for patients with NSCLC, 13.1 months for breast cancer, 6.3 months for GI cancers, 6.9 months for melanoma, and 11.5 months for RCC. Patients with NSCLC had longer survival times as compared to patients with breast ($P < 0.0001$), GI ($P < 0.0001$), melanoma ($P < 0.0001$), and RCC ($P < 0.0001$). Likewise, patients with breast cancer had longer median survival than patients with GI ($P = 0.005$) and RCC ($P = 0.04$). (B) Diagram of factors associated with prolonged survival for patients with different primary pathologies.

majority of the patient population, which is usually lung cancer in most studies.[3–9,15,17] These key differences make it important to separate patients with different primary cancers when attempting to identify factors associated with survival, as well as selecting treatment regimens.

Studies evaluating outcomes for patients with metastatic brain disease separated by primary cancers are few and limited.[10–13,18–23] Studies evaluating outcomes following surgical resection of these different primary cancers are even more sparse (Table 4).[10–13,18–21,24] These prior studies and others are limited because they included patients who did not undergo surgery,[10,23–26] only included solitary metastases,[18,23,27] contained a significant number of

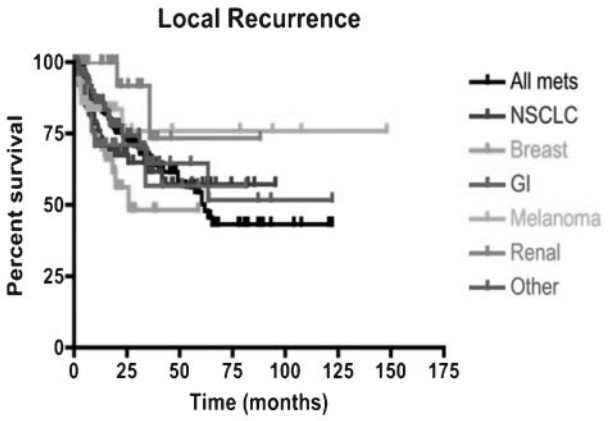

Figure 2 Local progression free survival (PFS) for patients with different primary cancers. Kaplan–Meier local PFS curves for patients separated by histology (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC). The 24-month local PFS rates for all patients was 74.3%, while the rate was 67.4% for patients with NSCLC, 56.2%, for breast cancer 70.9% for GI cancer, 75.9% for melanoma, and 91.7% for RCC. Patients with RCC had significantly longer local PFS rates than patients with NCSLC ($P = 0.02$), breast cancer ($P = 0.004$), and GI cancer ($P = 0.02$).

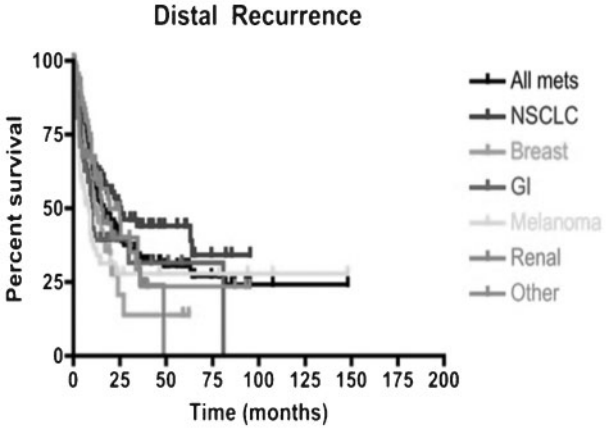

Figure 3 Distal progression free survival (PFS) for patients with different primary cancers. Kaplan–Meier distal PFS curves for patients separated by histology (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC). The median distal PFS for all patients was 15.7 months, while the median survival was 25.7 months for patients with NSCLC, 11.7 months for breast cancer, 9.7 months for GI cancers, 8.5 months for melanoma, and 15.2 months for RCC. Patients with NSCLC had significantly longer distal PFS rates than patients with breast ($P = 0.03$) and melanoma ($P = 0.002$).

patients who did not undergo adjuvant therapies,[12,13,19–21,27] and did not perform multivariate analyses.[11,18,24,26,27] As a result, the factors independently associated with survival for patients with different types of primary cancers remain unclear. This lack of clarity makes it difficult to prognosticate outcomes for patients with different types of primary cancers.

Differences between metastatic brain tumor patients with different primary cancers

There were significant differences in the pre, peri, and postoperative characteristics between the pathological groups in this study. Among the preoperative differences, the most notable were seen in the components used to assign RPA classification (age, primary tumor control, extracranial spread, KPS).[28] These key distinctions, as well as others found in this study, may make the RPA and other classification systems based on all patients with brain metastases less applicable or useful, especially for primary cancers that are less common.

In addition to these preoperative differences, there were also postoperative distinctions between different primary cancers. Patients with NSCLC and BC had the longest median survival. Rades *et al.* evaluated 195 patients who underwent surgery of a solitary metastasis, and found that a diagnosis of BC was independently associated with improved survival.[28] Tendulkar *et al.* studied 271 patients who underwent solitary metastatic tumor resection, and found that lung cancer was independently associated with improved survival.[29] These studies and others,

Table 3 Multivariate associations with prolonged survival for patients undergoing surgery of intracranial metastases separated by histology (non-small cell lung–NSCLC, breast, gastrointestinal–GI, melanoma, renal cell–RCC)

Multivariate associations with prolonged survival		
Variable	**Relative risk (95%CI)**	***P*-value**
NSCLC		
Female	0.610 (0.420–0.880)	0.008
RPA Class 1	0.549 (0.322–0.899)	0.02
Control of primary cancer	0.572 (0.387–0.851)	0.006
Solitary brain metastasis	0.520 (0.356–0.767)	0.001
Tumor size < 2 cm	0.680 (0.452–1.004)	0.05
Adenocarcinoma	0.598 (0.386–0.934)	0.02
Discharge to home	0.642 (0.421–0.992)	0.05
Post-op brain radiation	0.388 (0.266–0.570)	< 0.0001
Breast		
Age < 65 years	0.478 (0.258–0.954)	0.04
Lack of COPD	0.208 (0.072–0.880)	0.04
No skull base involvement	0.179 (0.053–0.820)	0.03
Post-op brain radiation	0.388 (0.221–0.714)	0.003
GI		
Age < 75 years	0.285 (0.112–0.838)	0.02
RPA Class < 3	0.080 (0.020–0.411)	0.005
KPS > 50	0.208 (0.072–0.754)	0.02
Lack of seizures	0.173 (0.068–0.514)	0.003
Lack of motor deficit	0.407 (0.218–0.747)	0.004
Non-esophagus primary	0.186 (0.062–0.631)	0.009
Non-hemorrhagic tumors	0.392 (0.195–0.832)	0.02
Avoidance of language deficit	0.053 (0.014–0.263)	0.002
Melanoma		
Lack of coronary artery disease	0.017 (0.001–0.399)	0.02
Seizures	0.377 (0.124–0.936)	0.03
Solitary metastasis	0.301 (0.175–0.515)	< 0.0001
Tumor size < 2 cm	0.562 (0.312–0.964)	0.03
Discharge to home	0.562 (0.312–0.964)	0.002
Post-op chemotherapy	0.383 (0.220–0.659)	0.0005
RCC		
KPS > 60	0.274 (0.110–0.782)	0.02
Avoidance of post-op ICH	0.274 (0.110–0.782)	0.02
Postoperative chemotherapy	0.278 (0.103–0.637)	0.008
All metastases		
Female	0.619 (0.513–0.748)	< 0.0001
RPA Class 1	0.683 (0.530–0.868)	< 0.0001
Lack of motor deficit	0.773 (0.637–0.941)	0.01
Lack of cognitive deficit	0.654 (0.525–0.820)	0.0003
Solitary brain metastasis	0.601 (0.494–0.733)	< 0.0001
Tumor size < 2 cm	0.711 (0.566–0.885)	0.002
Discharge to home	0.623 (0.502–0.777)	< 0.0001
Postoperative chemotherapy	0.726 (0.593–0.887)	0.002
Postoperative brain radiation	0.546 (0.448–0.666)	< 0.0001

however, are limited because they group all patients with metastatic tumors together and only include solitary lesions.[28,29] Large-scale studies attempting to evaluate differences in outcomes for patients with different primary cancers therefore remain unclear.

Factors independently associated with survival

Non-small cell lung cancer

It is estimated that 30–80% of patients with NSCLC will develop brain metastases.[3–9,17] Among brain metastases, NSCLC represents the most common source of primary cancers.[3–9,17] Once brain metastases develop, median survival is less than 6 months without treatment. Surgical resection and WBRT are associated with median survival times of 8–19 months.[20] Previous studies have found that the factors associated with shorter survival were: no surgery of their primary tumor, male gender, infratentorial location, extracranial spread, and age $>$ 60 years.[20] This study also found gender and radiation to be associated with survival, but also adds RPA Class, control of primary tumor, solitary brain metastasis, tumor size, adenocarcinoma, and discharge to home. This study also shows that among NSCLCs, adenocarcinomas have better prognoses than squamous cell carcinomas. This may be important because these histologies are typically grouped into the same NSCLC category.[4,15,30,31] In addition, solitary and smaller tumors were each independently associated with improved survival, which may signify less intracranial disease burden and thus improved survival.[32,33] Moreover, this study also emphasizes the importance of preserving functional status, where patients who were able to be discharged to home had improved survival.

Breast cancer

BC is the second most common cause of intracranial metastases.[34] It is estimated that 10–30% of patients with BC will develop brain metastases.[34] Median survival times vary from 5 to 16 months; however, the majority of these studies involved WBRT.[23,32,35] Niwinska and colleagues evaluated 100 patients with solitary BC metastases, and found that RPA Class 1, neurosurgical intervention, and chemotherapy were associated with improved survival.[23] Wronski *et al.* evaluated 70 patients and found that WBRT and absence of leptomeningeal disease were associated with improved survival.[21] The present study found that younger age, no skull base involvement, and postoperative brain radiation were associated with prolonged survival. Younger patients typically have a better ability to tolerate neurological insults associated with surgery, radiation, and chemotherapy.[4] Skull base lesions are relatively rare among patients with metastatic disease, and are typically treated with radiation therapy because of their presumed poor prognosis.[36] Lastly, as seen in previous primarily non-surgical studies, the use of postoperative radiation was associated with improved survival.[35]

Gastrointestinal cancer

Gastrointestinal cancers include a variety of different primary cancers including colorectal, hepatocellular, and gastric cancers.[37] These cancers metastasize less frequently to the brain, where approximately 2–4% of patients with these primary cancers will develop brain metastases.[37] The median survival for patients who develop brain metastases ranges from 4 to 8 months.[12,37] Jung *et al.* evaluated 126 patients, of which 20 underwent surgical resection.[38] In this

Table 4 Summary of previous surgical studies on intracranial metastases where different primary cancers were separately evaluated

Studies	Year	Non-surgical patients	No. surgical patients	NSCLC	Breast	RCC	Melanoma	GI
Present study	2012	No	708	X	X	X	X	X
Sundrasen *et al.*	1985	No	50	X				
Macchiarini *et al.*	1991	No	37	X				
Wronski *et al.**	1995	No	231	X				
Arbit *et al.**	1995	No	109	X				
Abrahams *et al.*	2001	Yes	50	X				
Wronski *et al.**	1997	No	70		X			
Niwinska *et al.*	2011	Yes	57		X			
Cahill *et al.*	2011	Yes†	264					
Wronski *et al.**	1996	No	50			X		
Salvati *et al.*	1992	No	29			X		
Shuch *et al.*	2008	Yes	48			X		
Wronski *et al.**	2000	No	91				X	
Zacest *et al*	2002	No	147				X	
Raizer *et al.**	2008	Yes	126				X	
Farnell *et al.*	1996	Yes	11					X
Wronski *et al.**	1999	No	73					X
Jiang *et al.*	2011	Yes	7					X
Noura *et al.*	2012	Yes	17					X
Jiang *et al.*	2012	Yes	6					X

* From the same institution. † Included patients who underwent spine surgery. GI = gastrointestinal; NSCLC = non-small cell lung cancer; RCC = renal cell cancer.

mixed treatment population, RPA class and chemotherapy were associated with prolonged survival.[38] Wronski *et al.* studied 73 patients operated on for metastatic colorectal carcinoma between 1974 and 1993, and found that only a cerebellar location was associated with poorer survival.[12] Among patients with GI primary cancers, younger age, lower RPA class, improved KPS, lack of preoperative motor deficit, non-esophageal tumors, non-hemorrhagic tumors, and lack of postoperative language deficits were independently associated with improved survival in this study. The most significant age, RPA class, and KPS associated with survival were 75, Class 3, and 50, respectively. These cutoffs are relatively low because it includes older patients and less functional patients than prior RPA grading systems.[4,15,33] Surgical intervention can therefore lead to improved outcomes for even GI patients with presumed poor prognoses.

Melanoma

Melanoma is considered the third most common type of cancer.[39] It is estimated that less than 10% of patients with melanoma will develop brain metastases.[39] However, brain involvement increases to 45–70% of patients with advanced melanoma.[39] Moreover, melanoma, unlike other cancers, has a greater propensity for micrometastases where patients can harbor numerous metastases without neurological symptoms.[39] The median survival ranges from 2 to 8 months in previous studies.[19,40] Raizer *et al.* evaluated 355 patients with melanoma, of which only 126 patients underwent surgery.[40] They found that age, number of intracranial metastases, extracranial spread, and presence of neurological symptoms were associated with poorer survival.[40] Wronski *et al.* from the same institution evaluated 91 patients who underwent intracranial melanoma resection, and reported similar findings.[19] This study found that preoperative seizures, solitary metastasis, smaller size tumors, discharge to home, and use of postoperative chemotherapy were independently associated with improved survival.

Renal cell cancer

RCC accounts for approximately 1–3% of all cancers.[41] Despite this relative rarity, it accounts for a significant number of intracranial metastases.[41] It is estimated that as high as 30% of patients with RCC will develop brain metastases.[41] The median survival times for patients who develop RCC brain metastases ranges from 4 to 23 months.[13,27,42] Salvati *et al.* evaluated 29 patients with solitary RCC who were operated on from 1975 to 1988, and found that radiation did not significantly improve survival.[27] Wronski *et al.* evaluated 50 patients operated on between 1974 and 1993, and found that a supratentorial location, lack of preoperative neurological deficit, and left-sided lesions were associated with prolonged survival.[13] This study found that preoperative KPS and use of postoperative chemotherapy were independently associated with prolonged survival.

Strengths and limitations

We believe this study provides several useful findings for patients who undergo surgical resection of intracranial metastases. First, studies comparing characteristics between patients with different primary cancers have yet to be done. This study shows there are important distinctions between patients with different primary cancers. These dissimilarities may preclude them from being included into the same study population. Second, studies attempting to obtain factors independently associated with survival for patients with different types of primary cancers are few and limited. The majority of these studies include patients who did not undergo surgical resection and/or had solitary metastases. These features are not necessarily applicable to most patients with metastatic disease. Lastly, this study may provide useful information that may help guide treatment strategies aimed at optimizing outcomes for patients with metastatic disease. This study shows that each primary cancer has different set of factors independently associated with survival. These factors can be taken into account when selecting optimal treatment regimens aimed at prolonging survival.

This study, however, has some limitations. One limitation is that these findings only apply to patients who underwent surgical resection of their intracranial metastasis. Second, this study was limited to patients with the most common types of primary cancer (lung, breast, GI, melanoma, and RCC). Patients with less common types of intracranial metastases were excluded from further analyses because of small patient numbers. Additionally, this study did not analyze the prognostic implication of molecular markers and genotypes including hormonal receptors, epidermal growth factor receptors, and HER-2, among others. These molecular markers may be better associated with survival for some types of primary cancer, but were not analyzed in this study. Furthermore, a significant number of patients in this study did not undergo GTR, WBRT, and/or SRS. The findings of this study may be altered in the context of receiving the most aggressive treatment regimens. Lastly, this study is inherently limited by its retrospective design. It is therefore not appropriate to infer direct causal relationships. However, we tried to create a uniform patient population by utilizing strict inclusion criteria in order to provide more relevant information for patients who underwent intracranial metastatic tumor surgery. We also performed multivariate analyses to control for potential confounding variables. Given these statistical

controls and relatively precise outcome measures, we believe our findings offer useful insights into the management of patients with different types of primary cancers. However, prospective studies are ultimately needed to provide better data to guide clinical decision-making.

Conclusions

Patients with a variety of different primary cancers can develop intracranial metastases. When patients with different primary cancers develop metastatic disease to body sites, they are not grouped into the same category. It is therefore peculiar why patients who develop intracranial metastases are all lumped together. This study shows that patients with different types of primary cancers have disparate patient-related characteristics and factors independently associated with survival. Patients with different primary cancers who develop intracranial metastases therefore represent distinct clinical groups with disparate characteristics and outcomes, and should be studied according to their primary cancer and not their metastatic site.

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None

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