

Survival and Recurrence for Patients Undergoing Surgery of Skull Base Intracranial Metastases

Kaisorn L. Chaichana^{1,2} Mariana Flores^{1,2} Shami Acharya^{1,2} Paul Sampognaro^{1,2}
 Chetan Bettegowda^{1,2} Daniele Rigamonti^{1,2} Jon D. Weingart^{1,2} Alessandro Olivi^{1,2} Gary L. Gallia^{1,2}
 Henry Brem^{1,2} Michael Lim^{1,2} Alfredo Quinones-Hinojosa^{1,2}

¹Departments of Neurosurgery, Johns Hopkins University, Neuro-Oncology Outcomes Laboratory, Baltimore, Maryland, USA
²Departments of Oncology, Johns Hopkins University, Neuro-Oncology Outcomes Laboratory, Baltimore, Maryland, USA

Address for correspondence Kaisorn L. Chaichana, MD, Department of Neurosurgery, The Johns Hopkins Hospital, Johns Hopkins University, 600 North Wolfe Street, Meyer 8-184, Baltimore, MD 21202 USA (e-mail: Kaisorn@jhmi.edu).

J Neurol Surg B 2013;74:228–235.

Abstract

Objective Skull base metastases (SBMs) are rare lesions in close proximity to critical neural and vasculature structures. This rarity and complexity have led many to only offer nonsurgical therapies. The surgical outcomes for patients with SBM therefore remain unknown.

Design Retrospective, comparison analyses.

Setting Johns Hopkins Hospital.

Participants All patients who underwent intracranial metastatic tumor surgery.

Main Outcome Measure Survival and recurrence.

Results Of the 708 patients who underwent intracranial metastatic tumor surgery, 29 (4%) had SBM: 3 (10%) involved the anterior skull base, 7 (24%) the sella, 6 (21%) the orbit, 2 (7%) the sphenoid wing, 3 (10%) the clivus, 4 (14%) the petrous bone, and 4 (14%) the paranasal sinuses. Following surgery, 6 (50%) had improvements in vision and 14 (88%) had improvement and/or maintenance of their cranial nerve symptoms. Three (10%), 0(0%), and 1(3%) developed a new motor, language, and vision deficit, respectively. There were no differences in median survival (10.0 versus 9.2 months, $p = 0.48$) and local progression-free survival (PFS) ($p = 0.52$), but there was improved distal PFS ($p = 0.04$) between patients with and without SBM.

Conclusions Patients with SBM are relatively rare. These patients can tolerate surgery with minimal morbidity and mortality, and they have similar prognoses to patients without SBM.

Keywords

- metastatic brain tumor
- recurrence
- skull base
- surgery
- survival

Introduction

The most common type of brain malignancy in adults is metastatic brain tumors.^{1,2} It is estimated that 25 to 45% of patients with cancer develop metastatic brain lesions each year.¹ Further exacerbating this issue is that patients are surviving longer with cancer as a result of developments in surgical therapy, chemotherapeutic options, and radiation

therapy.^{2–6} This has resulted in patients presenting with more numerous intracranial metastases and/or atypical location of their metastases.^{3,7} An uncommon location for metastases is the skull base.^{8,9} Skull base metastases (SBMs) are challenging to manage because they are rare and develop in close proximity to several critical neural and vascular structures. This rarity and complexity have precluded defining optimal treatment for patients who present with SBM.

received
 November 13, 2012
 accepted after revision
 January 28, 2013
 published online
 April 3, 2013

© 2013 Georg Thieme Verlag KG
 Stuttgart · New York

DOI <http://dx.doi.org/10.1055/s-0033-1342925>.
 ISSN 2193-6331.

Patients who present with SBM are rarely offered surgical therapies, unlike patients with intracranial metastases elsewhere.^{10–12} Patients with SBM are typically only offered radiation therapy in the form of stereotactic radiosurgery, whole-brain radiation, or proton beam therapy.^{6,10–13} Surgical interventions are withheld because the surgical outcomes for patients with SBM remain unclear. The goals of this study were to therefore (1) ascertain the proportion of patients who underwent surgery of a SBM, (2) understand the clinical differences between patients who develop SBM and non-SBM, and (3) understand the survival and recurrence outcomes for this group of patients who undergo surgical resection. A better understanding of these characteristics may better define if surgery is a viable option for this uncommon subset of patients, which are usually offered only nonsurgical therapies.^{10–12}

Methods

Approval was obtained from the Institutional Review Board (36875) prior to the start of this study.

Patient Selection and Recorded Variables

All adult patients (age > 18 years) ($n = 708$) who underwent needle biopsy and/or surgical resection of an intracranial metastasis between 1997 and 2011 were retrospectively reviewed. This included patients undergoing resection of a single or multiple intracranial metastases. Among these patients, patients who underwent surgical resection of a SBM were identified. A SBM was defined as involvement of the bone of the skull base by pathology-proven metastasis (► **Figs. 1** and **2**). This included metastases involving bone of the anterior cranial fossa, orbit, sella, sphenoid wing and paranasal sinuses, clivus, and petrous bone. Metastases involving the cerebellopontine angle were not included. Metastases were classified based on where the tumor was believed to primarily originate. The pathology was determined by a senior neuropathologist in all cases. Primary

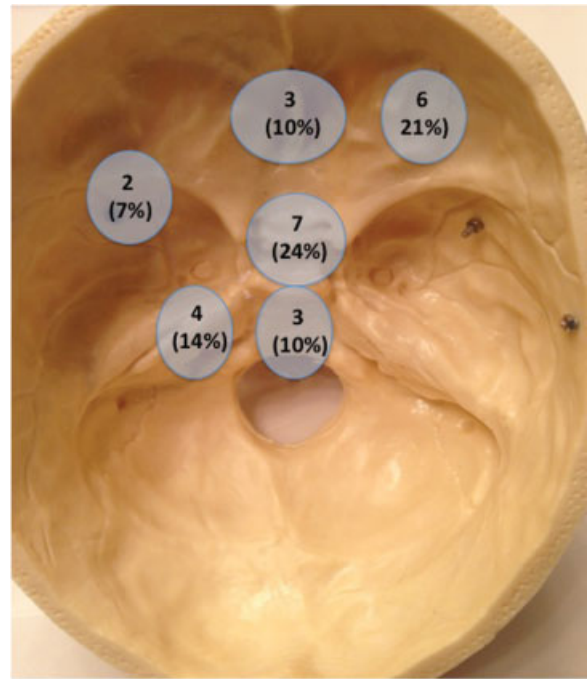


Fig. 2 Distribution of skull base metastases in this study.

tumors that locally infiltrated the skull base, rather than distally metastasized, were excluded.

The information collected from neurosurgery and neuro-oncology clinical notes included patient demographics, comorbidities, presenting symptoms, brain and body imaging characteristics, postoperative neurological function, and adjuvant therapy. Patients were assigned a Karnofsky performance scale (KPS) index¹⁴ and recursive partitioning analysis (RPA) classification group¹⁵ by a reviewer blinded to patient outcomes at the clinic visit prior to surgery during a chart review. The presence of a motor deficit was defined as decreased strength, a language deficit as any combination of receptive and/or expressive aphasia, a cognitive deficit as

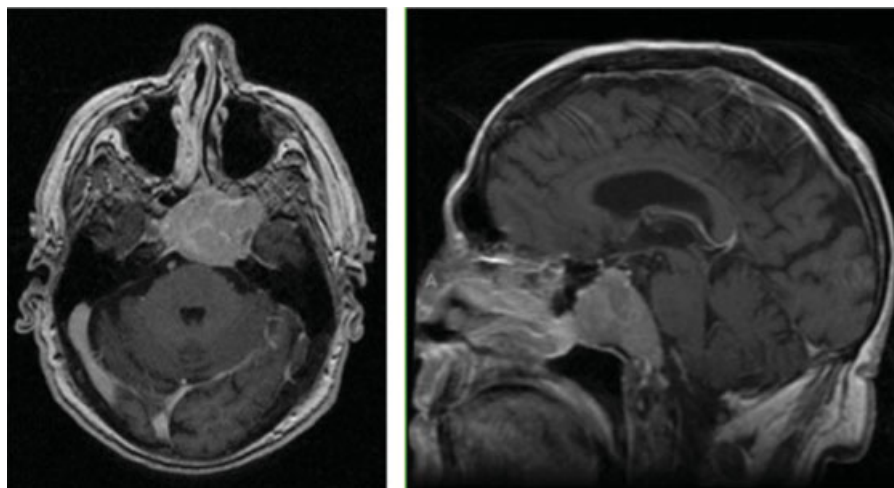


Fig. 1 Example of a patient with a skull base metastasis. This is a 58-year-old man with a history of non-small cell lung cancer who presented with a solitary metastasis primarily involving the clivus and sphenoid sinus.

any complaint of decreased mental status or ability, and a vision deficit as any decrease in visual acuity or visual field perception.

All patients underwent preoperative and postoperative magnetic resonance imaging (MRI). The characteristics that were recorded included the lesion's size (largest diameter based on gadolinium enhancement), specific lobe involvement, number of intracranial metastases, and presence of hydrocephalus. Extent of resection was determined by comparing preoperative and postoperative MRIs obtained < 48 hours after surgery as gross total resection (GTR) if no residual enhancement, near-total resection (NTR) if only a rim of enhancement is seen in the resection cavity, or subtotal resection (STR) if residual nodular enhancement was noted on postoperative MRI.¹⁶ The presence of dilated ventricles with transependymal flow was used to classify the presence of hydrocephalus. In addition to neuro-imaging, all patients underwent computed tomography (CT) scans of the chest, abdomen, pelvis, and spine with oral and intravenous contrast to identify control of primary tumor and presence of extracranial spread.

Outcome Variables

Survival data was obtained from the Social Security Death Index database.¹⁷ Survival time was calculated from time of surgery to death. Patients whose deaths were unconfirmed were classified as lost to follow-up at the time of their last clinic visit. Local recurrence was noted when there was recurrence or progression of tumor in the previous surgical cavity. Distal recurrence was noted when new tumor not present at the time of surgery appeared in the brain not adjacent to the previous surgical cavity. Local and distal progression-free survival (PFS) times were calculated from the time of surgery to MRI evidence of local and distal recurrence, respectively. Patients whose recurrence was unconfirmed were classified as lost to follow-up at the time of their last neuroimaging.

General Treatment Strategy

Surgery was generally advocated for patients with intracranial metastases without a diagnosis or for lesions causing symptoms due to location or swelling. For all surgically resectable tumors, the general aim was to achieve GTR of the tumor when possible. STR was achieved typically when the tumor involved eloquent brain or critical neurovascular structures as confirmed by intraoperative mapping and/or monitoring (awake/speech language mapping, direct cortical motor stimulation, and motor-evoked or somatosensory-evoked potentials). Surgery was pursued for multiple metastases when the metastases were easily accessible and/or causing symptoms. Motor-evoked and somatosensory-evoked potentials were used in the majority of cases, and surgical navigation (CT and/or MRI wand) was used in all cases after 2001.

Postoperative MRI with gadolinium was typically performed at 3-month intervals following surgery or when symptoms developed. In regards to adjuvant therapy, the uses of radiation therapy, including whole-brain radiation

(WBRT) and/or stereotactic radiosurgery (SRS), as well as chemotherapy, were determined by a multidisciplinary team (neurosurgery, neuro-oncology, medical oncology, and radiation oncology) and the patients and their families.

Statistical Analysis

Summary data were presented as mean \pm standard deviation for parametric data and as median (interquartile range [IQR]) for nonparametric data. For intergroup comparisons between patients with SBM and non-SBM, student's *t*-test was used for continuous data and Fisher exact test for categorical data. Survival, local recurrence, and distal recurrence as a function of time were plotted using the Kaplan-Meier method, and Log-rank analysis was used to compare plots (GraphPad Prism 5, La Jolla, California, USA). Values with *p* < 0.05 in these analyses were considered statistically significant. JMP 9 (SAS, Cary, North Carolina, USA) was used unless otherwise specified.

Results

Preoperative Characteristics of All Patients

The preoperative characteristics of the 708 adults patients in this study are summarized in ►Table 1. Out of the 708 patients who underwent surgery for an intracranial metastasis, 29 (4%) presented with a SBM. The average age of the entire population at the time of surgery was 58.4 ± 12.1 years. A total of 336 (47%) patients were male, and the major presenting symptoms were headaches in 293 (41%), motor deficits in 254 (36%), cognitive deficits in 146 (21%), vision deficits in 120 (17%), language deficits in 111 (16%), and seizures in 110 (16%). The median (IQR) preoperative KPS of these patients was 80 (70 to 80), and 152 (21%), 421 (59%), and 135 (19%) patients presented with an RPA class of 1, 2, and 3, respectively. The average size of the operated tumor was 3.2 ± 1.5 cm, and 256 (36%) involved the frontal lobe, 154 (22%) the parietal lobe, 102 (14%) the temporal lobe, 101 (14%) the occipital lobe, and 140 (20%) the cerebellum. The median (IQR) number of intracranial metastases was 1 (1 to 2).

Perioperative and Postoperative Characteristics of All Patients

The perioperative and postoperative outcomes are summarized in ►Table 2. 80 (11%) patients underwent resection of multiple intracranial metastases. GTR of the resected lesions was achieved in 502 (71%) patients. Perioperatively, 65 (9%), 10 (1%), and 16 (2%) developed a new motor, language, and vision deficit, respectively. Thirteen (2%) patients developed a wound infection, and 10 (1%) had an intracranial hemorrhage requiring operative evacuation. A total of 249 (35%) patients underwent postoperative chemotherapy, and 449 (63%) underwent radiation therapy. Among patients who underwent radiation therapy, 340 (76%) underwent WBRT and 222 (49%) underwent SRS. At last follow-up, 51 (7%) patients developed leptomeningeal disease.

In this study, 514 (73%) patients died, 107 (15%) developed local recurrence, and 226 (32%) developed distal recurrence

Table 1 Preoperative Characteristics of Patients Undergoing Surgery of Skull Base and Nonskull Base Intracranial Metastases from 1997 to 2011.

Study population (n = 708)			
Characteristics	Skull base metastases N = 29	Nonskull base metastases N = 679	p value
Demographics			
Age ^a	58.4 ± 13.1	58.4 ± 12.0	0.99
Male	14 (48%)	322 (47%)	0.99
KPS ^b	80 (70–90)	80 (70–80)	0.49
Headaches	7 (24%)	286 (42%)	0.06
Seizures	0 (0%)	110 (16%)	0.01
Motor deficit	2 (7%)	252 (37%)	0.0005
Language deficit	2 (7%)	109 (16%)	0.29
Cognitive deficit	4 (14%)	142 (21%)	0.48
Vision deficit	12 (41%)	108 (16%)	0.001
Tumor characteristics			
Control of primary	16 (55%)	486 (72%)	0.06
Extracranial spread	11 (38%)	313 (46%)	0.45
No. of metastatic body met sites ^b	1 (1–2)	1 (1–3)	0.71
RPA class	4 (14%)	148 (22%)	0.36
RPA class 1	18 (62%)	403 (59%)	0.85
RPA class 2	7 (24%)	128 (19%)	0.47
RPA class 3	22 (76%)	438 (65%)	0.24
Solitary metastasis			
Primary tumor			
NSCLC	11 (38%)	259 (38%)	0.99
SCLC	2 (7%)	31 (5%)	0.39
Breast cancer	7 (24%)	99 (15%)	0.18
GI cancer	2 (7%)	70 (10%)	0.76
Melanoma	1 (3%)	87 (13%)	0.24
Renal cell cancer	0 (0%)	51 (8%)	0.26
Primary bone cancer	4 (14%)	13 (2%)	0.004
Thyroid	1 (3%)	8 (1%)	0.05
Unknown	1 (3%)	8 (1%)	0.05
Other	0 (0%)	53 (8%)	0.16
Radiographics			
Tumor size ^a	3.1 ± 1.6	3.2 ± 1.5	0.86
No. of brain mets ^b	1 (1–1)	1 (1–2)	0.18
Hemorrhagic	3 (10%)	135 (20%)	0.34

Abbreviations: KPS, Karnofsky performance score; NSCLC, non-small cell lung cancer; RPA, recursive partitioning analysis; SCLC, small cell lung cancer.

Note: The bolded values are statistically different from one or more of the other histological groups ($p < 0.05$).

^amean ± standard deviation

^bmedian (interquartile range).

at last follow-up. The median survival of the entire cohort was 9.3 months, with 6-, 12-, and 24-month survival rates of 61%, 42%, and 26%, respectively. The 6-, 12-, and 24-month local PFS rates were 87%, 77%, and 69%, respectively. The median distal PFS was 15.7 months, with 6-, 12-, and 24-month distal progression free survival rates of 72%, 55%, and 42%, respectively. The median (IQR) follow-up time for surviving patients was 10.2 (2.8 to 22.8) months.

Differences between Patients Undergoing Surgery for Skull Base and Nonskull Base Metastases

The differences between patients undergoing resection of SBM and non-SBM are summarized in ►Tables 1 and 2. Preoperatively, patients undergoing resection of a SBM

more commonly presented with visual deficits ($p = 0.001$) and, less commonly, seizures ($p = 0.01$) and motor deficits ($p = 0.0005$). Moreover, patients with SBM more commonly had primary bone cancers ($p = 0.004$), thyroid cancers ($p = 0.05$), and unknown primary cancers ($p = 0.05$). There were no differences between the cohorts in regards to age, KPS, control of primary extracranial spread, and RPA classification group.

Perioperatively, patients who underwent SBM resection less commonly underwent GTR ($p = 0.0001$) and more commonly underwent NTR ($p = 0.01$) and STR ($p = 0.03$). There were no statistical differences in the number of metastases resected, occurrence of iatrogenic deficits, development of leptomeningeal disease, and use of adjuvant therapies

Table 2 Perioperative and Postoperative Characteristics of Patients Undergoing Skull Base and Nonskull Base Intracranial Metastases from 1997 to 2011.

Study population (n = 708)			
Characteristics	Skull base metastases N = 29	Nonskull Base metastases N = 679	p value
Surgery			
Gross total resection	10 (34%)	492 (72%)	0.0001
Near total resection	11 (31%)	117 (17%)	0.01
Subtotal resection	6 (21%)	54 (8%)	0.03
Biopsy	2 (7%)	16 (2%)	0.17
Multiple mets resected	1 (3%)	79 (12%)	0.24
New symptoms			
Motor deficit	3 (10%)	62 (9%)	0.74
Language deficit	0 (0%)	20 (3%)	0.99
Vision deficit	1 (3%)	15 (2%)	0.49
Adjuvant therapy			
Chemotherapy	9 (31%)	240 (35%)	0.70
Radiation therapy	19 (66%)	430 (63%)	0.99
Whole-brain XRT	10 (34%)	330 (49%)	0.18
Stereotactic XRT	9 (31%)	213 (31%)	0.99
Complications			
Wound infection	2 (7%)	11 (2%)	0.10
Intracranial hemorrhage	0 (0%)	10 (1%)	0.99
Leptomeningeal disease	2 (7%)	49 (7%)	0.99
DVT/PE	2 (7%)	27 (4%)	0.34
Pneumonia	0 (0%)	29 (4%)	0.63
Survival			
Deaths	18 (62%)	496 (73%)	0.20
Median survival	10.0	9.2	0.48
Local recurrence	6 (21%)	101 (15%)	0.42
12-month local PFS rate	75.0%	76.8%	0.52
Distal recurrence	5 (17%)	221 (33%)	0.10
12-month distal PFS rate	82.9%	53.4%	0.04

Abbreviations: DVT, deep vein thrombosis; PE: pulmonary embolism; PFS: progression free survival; XRT, radiation therapy.

Note: The bolded values are statistically different from one or more of the other histological groups ($p < 0.05$).

including chemotherapy and radiation therapy among patients who underwent SBM and non-SBM resection.

At last follow-up, patients undergoing SBM resection had no difference in overall survival times ($p = 0.20$) or local PFS ($p = 0.52$) as compared with patients with non-SBM. However, patients with SBM had longer median distal PFS rates than patients with non-SBM (82.9% versus 53.4%, $p = 0.04$).

Perioperative Outcomes for Patients with Skull Base Metastases

Metastases were located along the floor of the frontal bone in three patients (10%) with SBM, in the sellar/suprasellar region in seven (24%), the orbital region in six (21%), the sphenoid wing in two (7%), the clivus in three (10%), the petrous bone in four (14%), and the paranasal sinuses in four (14%) (►Figs. 1 and 2). Among patients with SBM, 16 (55%) presented with cranial nerve deficits: 6 (38%) had deficits of cranial nerve II; 4 (25%) with cranial nerve III, IV, or VI; 3 (19%) with cranial nerve V; and 6 (38%) with cranial nerve VII. Following surgery, three (50%) had improvements in vision among those with

visual complaints, and seven (44%) and seven (44%) had improvements and maintenance of their cranial nerve symptoms among those with cranial nerve deficits, respectively. Three (10%) developed a new motor deficit, none (0%) had new language deficit, one (3%) had new vision deficit, and two (7%) had a new cranial nerve deficit. The patient with a new vision deficit had decreased visual acuity where their eye vision went from 20/25 to 20/200. The other patient who developed new cranial nerve deficit developed a new cranial nerve III deficit.

Survival for Patients with Skull Base Metastases

At last follow-up, 18 (62%) patients with SBM died as compared with 496 (73%) patients with non-SBM ($p = 0.20$) (►Fig. 3). The median survival for patients with SBM was 10 months versus 9.2 months for patients with non-SBM ($p = 0.48$). The 6-, 12-, 24-, and 36-month survival rates for patients with SBM were 58.4%, 49.3%, 38.4%, and 23.0%, respectively. The 6-, 12-, 24-, and 36-month survival rates for patients with non-SBM were 60.8%, 41.2%, 25.6%, and 17.4%, respectively ($p = 0.48$).

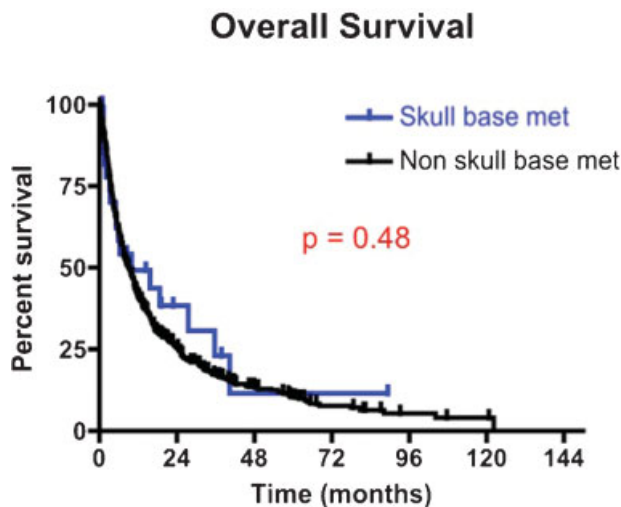


Fig. 3 Kaplan-Meier survival curves for patients undergoing intracranial surgery of a skull base metastasis versus nonskull base metastases between 1997 and 2011. The median survival for patients with skull base metastases was 10.0 months versus 9.2 months for patients with nonskull base metastases ($p = 0.48$).

Local PFS for Patients with Skull Base Metastases

At last follow-up, 6 (21%) patients with SBM incurred local recurrence as compared with 101 (15%) patients with non-SBM ($p = 0.42$) (► Fig. 4). The 6-, 12-, 24-, and 36-month local PFS rates for patients with SBM were 81.8%, 75.0%, 56.3%, and 56.3%, respectively. In comparison, the 6-, 12-, 24-, and 36-month local PFS rates for patients with non-SBM were 86.7%, 76.8%, 69.7%, and 62.0%, respectively ($p = 0.52$).

Distal Progression Free Survival for Patients with Skull Base Metastases

At last follow-up, 5 (17%) patients with SBM incurred recurrence at a distal intracranial site as compared with 221 (33%) patients with non-SBM ($p = 0.10$) (► Fig. 5). The 6-, 12-, 24-,

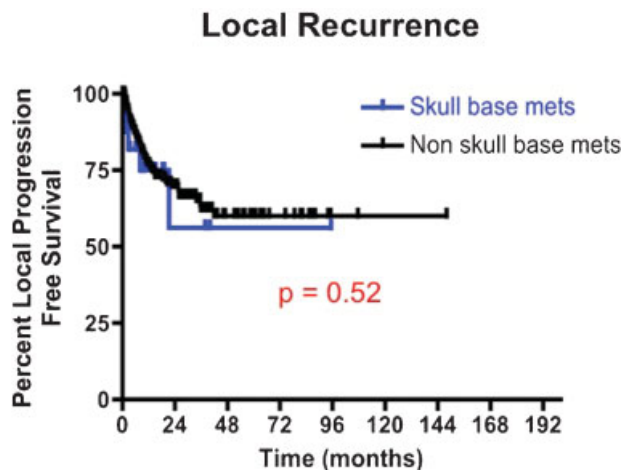


Fig. 4 Kaplan-Meier local progression-free survival curves for patients undergoing intracranial surgery of a skull base metastasis versus nonskull base metastases between 1997 and 2011. The 12-month local progression-free survival rate for patients with skull base metastases was 75.0% versus 76.8% for patients with nonskull base metastases ($p = 0.52$).

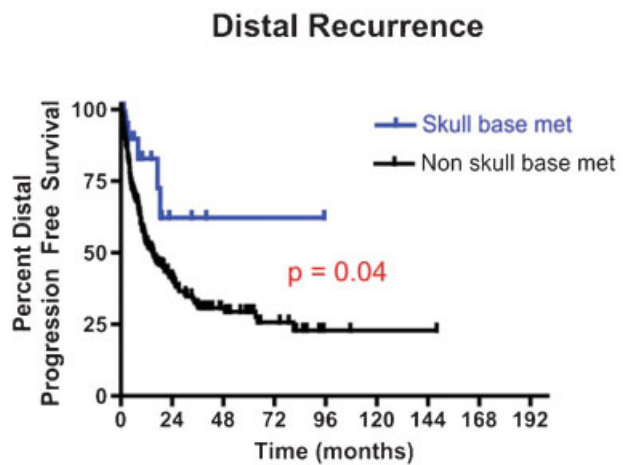


Fig. 5 Kaplan-Meier distal, intracranial progression-free survival curves for patients undergoing intracranial surgery of a skull base metastasis versus nonskull base metastases between 1997 and 2011. The 12-month distal, intracranial progression-free survival rate for patients with skull base metastases was 82.9% versus 53.4% for patients with nonskull base metastases ($p = 0.04$).

and 36-month distal PFS rates for patients with SBM were 89.8%, 82.9%, 62.2%, and 62.2%, respectively. In comparison, the 6-, 12-, 24-, and 36-month local PFS rates for patients with non-SBM were 70.8%, 53.4%, 40.9%, and 31.6%, respectively ($p = 0.04$).

Discussion

Patients with SBM represent a rare subgroup of patients with intracranial metastases.¹⁰⁻¹² In this study, 29 (4%) patients underwent surgery for a SBM during the reviewed period. Patients with SBM more commonly presented with vision deficits, primary bone cancers, thyroid cancers, and unknown primary cancers, unlike patients with non-SBM. Moreover, patients with SBM less frequently had seizures and motor deficits. Perioperatively, patients with SBM less commonly underwent GTR but more commonly had NTR. Among patients with SBM, seven (44%) reported improvement in cranial nerve symptoms and four (14%) reported a new iatrogenic deficit. At last follow-up, there were no significant differences between SBM and non-SBM patients in regards to overall survival and local PFS, but SBM had improved distal PFS.

The brain is a common metastatic site for several types of primary cancers.¹ The overwhelming majority of these intracranial metastases involve the brain parenchyma.¹ However, a small subset may also involve the skull base.¹⁰⁻¹² The skull base is in close proximity to several critical neural and vascular elements, which if damaged can cause significant morbidity and mortality. This rarity and proximity to critical structures have made many refrain from offering surgery to patients with SBM, even though patients with other intracranial metastatic locations frequently undergo surgery.¹⁰⁻¹²

Prior studies on SBM are few and limited (► Table 3).¹⁰⁻¹² Mori et al studied the effects of stereotactic radiosurgery on cranial nerve improvements for 11 patients who presented

Table 3 Summary of Studies on Metastases Involving the Skull Base

Studies	Year	No. patients with skull base metastases	Included nonskull base metastases	Included surgical patients
Present study	2012	29	No	Yes
Pan et al ¹¹	2012	27	Yes	No
Mori et al ¹⁰	2010	11	No	No
Tokuuye et al ¹²	1998	6	Yes	No

with cranial nerve deficits and SBM.¹⁰ The median survival for these patients was 16 months, and 1 (9%) had local recurrence.¹⁰ More importantly, 10 of 11 patients reported improvements in cranial nerve symptoms after radiation treatment.¹⁰ Pan et al evaluated the effects of gamma knife radiosurgery on 43 patients with skull base malignancies, of which 27 had metastases.¹¹ Patients with SBM had shorter median survival than patients with primary malignancies of the skull base (15 months versus 47 months).¹¹ Tokuuye and colleagues studied the role of fractionated radiation in 64 patients, of which 6 had skull base tumors.¹² In this heterogeneous population, better survival was seen in patients with tumors < 5 cm in diameter and/or three or fewer intracranial metastases.¹² The pathology of these skull base tumors, however, was not reported.¹²

Patients with SBM had different presenting symptoms than patients without SBM. Patients with SBM more commonly presented with vision deficits, and less frequently seizures and motor deficits. This makes intuitive sense as these skull base tumors are in close proximity to the optic nerve, thus more commonly causing vision deficits. Likewise, SBM are not nearby areas commonly responsible for seizures and motor deficits, including cortical regions, mesial temporal lobe, and perirolandic areas.^{18,19} These differences in location most likely account for the differences seen in presenting symptoms between patients with and without SBM.

It remains unclear which tumors more commonly metastasize to the skull base because studies comparing pathology of SBM to non-SBM have yet to be done. Pan et al had 27 patients with SBM who underwent radiation therapy.¹¹ The most common SBMs were breast cancer in seven (26%), nasopharyngeal carcinoma in five (19%), lung cancer in four (15%), thyroid cancer in one (4%), and unknown cancer in one (4%).¹¹ Mori et al had 11 patients in their study, and 5 (45%) had breast cancer, 3 (27%) had gastrointestinal cancers, and 1 (9%) each had renal cell cancer, melanoma, and prostate cancer.¹⁰ The present study primarily comprised patients with lung cancer, breast cancer, and primary bone cancer. However, the proportion of patients with thyroid cancer, primary bone malignancies, and unknown cancers had a larger frequency of SBM as compared with non-SBM.

Patients with SBM are rarely offered aggressive surgery.¹⁰⁻¹³ It is presumed that these patients do not do well as compared with primary skull base malignancies.¹⁰⁻¹³ It is also assumed that they have a poorer prognosis than patients with non-SBM.¹⁰⁻¹³ These assumptions are most likely due to their rarity. In this study, 21 (72%) patients underwent radical

resection (GTR or NTR). Despite this, there was no increase in frequency of iatrogenic deficits. Moreover, many of the patients in this study experienced improvement in symptoms following surgical resection. This study thus advocates for aggressive surgical resection of SBM, as with non-SBM, when it is safe to do so.

The long-term outcomes for patients with SBM remain unclear because there is a paucity of studies.¹⁰⁻¹³ In this study, the overall survival and local PFS were not significantly different between patients with and without SBM. However, the distal PFS was significantly longer for patients with SBM. This improved distal PFS among patients with SBM may be due to their primary extra-axial location along the skull base. This location may minimize seeding of cerebrospinal fluid pathways during surgery and/or tumor growth. Additionally, this discrepancy may be due to differences in tumor pathology, where tumors that acquire the ability to metastasize to intra-axial areas have a higher propensity to metastasize to other intracranial areas than do SBM. Nonetheless, patients with SBM do not have a worse outcome following surgery than patients with non-SBM. Surgery can also result in improvement in symptoms.

Strength and Limitations

We believe this study provides several useful insights for patients with SBM. First, the outcomes for patients with SBM who undergo surgical resection are unclear. Studies on SBM are limited and only evaluate the effects of radiation therapy.¹⁰⁻¹³ Second, this study is the first to compare surgical outcomes for patients with SBM and non-SBM. This study shows that surgery can be pursued with no increase in perioperative morbidity and mortality as compared with patients with non-SBM. Third, this study compared long-term outcomes for patients with SBM and non-SBM. This study shows there are no survival and/or local recurrence differences between patients undergoing surgery for a SBM or non-SBM. Patients with SBM, however, may have improved distal PFS than non-SBM patients. Lastly, this study may provide useful information that may help guide treatment strategies aimed at prolonging survival and delaying recurrence for patients with SBM. These patients, if offered surgery, can have improvement in symptoms and survival outcomes that rival patients without SBM.

This study, however, has some limitations. One limitation is that these findings only apply to patients undergoing surgery for SBM. Patients who did not undergo surgery were excluded, and patients with primary tumors that

invaded the skull base were not considered. Patients who were offered surgery for their SBM are likely self-selected to have good outcomes as compared with patients who were not offered surgery. Patients who were not offered surgery were not included in this study. This study was also underpowered to perform multivariate analyses to identify clinical factors associated with survival and recurrence. Larger studies may be necessary to identify these factors, but national databases may be required given the rarity of these lesions. Moreover, this study does not evaluate the effects of surgical approaches. This study was intended to evaluate long-term outcomes for a subset of patients with SBM, and not use of skull base approaches. Furthermore, the patients in this study underwent disparate treatment regimens. A significant number of patients in this study did not undergo WBRT, SRS, and/or chemotherapy. Mori et al found good results in terms of survival and cranial nerve symptoms for patients with SBM and SRS.¹⁰ Patients in this study were not routinely offered SRS because of close proximity and potential endangerment of cranial nerves. The results of this study may be altered in the context of patients receiving more aggressive therapies. Finally, this study is inherently limited by its retrospective design. This design means that there may be an inherent bias associated with patient selection, where patients who were offered surgery may have a propensity for better outcomes. However, we tried to create a uniform patient population by utilizing strict inclusion criteria, thus providing more relevant information for patients undergoing surgery for a SBM. Given these criteria and relatively precise outcome measures, we believe our findings offer useful insights into outcomes for patients with SBM. However, prospective studies are needed to provide better data to guide clinical decision-making.

Conclusion

Patients with SBM are a rare subset of patients with intracranial metastases. These tumors are in close proximity to critical neural and vascular structures. Their rarity and close proximity to critical structures have made many tend to refrain from offering aggressive surgical therapies. This study highlights the findings that patients with SBM can be treated aggressively without an increase in morbidity and mortality and have survival and recurrence rates that are comparable to patients with non-SBM. Patients with SBM should therefore be considered for aggressive therapies.

Acknowledgments

CLC was supported the NIH T32 Training Grant.

References

- Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist* 2007;12(7):884–898
- Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. *J Natl Compr Canc Netw* 2008;6(5):505–513, quiz 514
- Claus EB. Neurosurgical management of metastases in the central nervous system. *Nat Rev Clin Oncol* 2012;9(2):79–86
- Ewend MG, Williams JA, Tabassi K, et al. Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. *Cancer Res* 1996;56(22):5217–5223
- Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res* 2007;13(12):3637–3641
- Frazier JL, Batra S, Kapor S, et al. Stereotactic radiosurgery in the management of brain metastases: an institutional retrospective analysis of survival. *Int J Radiat Oncol Biol Phys* 2010;76(5):1486–1492
- Grossman R, Mukherjee D, Chang DC, et al. Predictors of inpatient death and complications among postoperative elderly patients with metastatic brain tumors. *Ann Surg Oncol* 2011;18(2):521–528
- Barajas RF Jr, Cha S. Imaging diagnosis of brain metastasis. *Prog Neurol Surg* 2012;25:55–73
- Delattre JY, Krol G, Thaler HT, Posner JB. Distribution of brain metastases. *Arch Neurol* 1988;45(7):741–744
- Mori Y, Hashizume C, Kobayashi T, Shibamoto Y, Kosaki K, Nagai A. Stereotactic radiotherapy using Novalis for skull base metastases developing with cranial nerve symptoms. *J Neurooncol* 2010;98(2):213–219
- Pan J, Liu AL, Wang ZC. Gamma knife radiosurgery for skull base malignancies. *Clin Neurol Neurosurg* 2013;115(1):44–48
- Tokuuye K, Akine Y, Sumi M, et al. Fractionated stereotactic radiotherapy of small intracranial malignancies. *Int J Radiat Oncol Biol Phys* 1998;42(5):989–994
- Pommier P, Liebsch NJ, Deschler DG, et al. Proton beam radiation therapy for skull base adenoid cystic carcinoma. *Arch Otolaryngol Head Neck Surg* 2006;132(11):1242–1249
- Dutta D, Vanere P, Gupta T, Munshi A, Jalali R. Factors influencing activities of daily living using FIM-FAM scoring system before starting adjuvant treatment in patients with brain tumors: results from a prospective study. *J Neurooncol* 2009;94(1):103–110
- Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;37(4):745–751
- McGirt MJ, Chaichana KL, Gathinji M, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. *J Neurosurg* 2009;110(1):156–162
- Social Security Death Index Database Available at: <http://searches.rootsweb.ancestry.com/>. Accessed March 22, 2013.
- Chaichana KL, Parker SL, Olivi A, Quiñones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. *J Neurosurg* 2009;111(2):282–292
- Chaichana KL, Pendleton C, Zaidi H, et al. Seizure Control for Patients Undergoing Meningioma Surgery. *World Neurosurg* 2012