

Pituitary Metastases Experience in a Neurosurgical Oncology Cohort

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Abstract: Previously reported prevalence of pituitary metastases ranges from 0.4-5%. This study's primary objective is to determine the incidence of pituitary metastases among patients presenting for neurosurgical evaluation with abnormal pituitary imaging findings, and secondarily to report our outcomes. We conducted a single-center, retrospective chart review of patients undergoing neurosurgical evaluation for sellar/suprasellar masses from 2008-2020. Demographic data, presenting symptoms, radiographic features, interventions, and outcomes were analyzed. 78 charts were reviewed; 21 patients (26.9%) had history of prior cancer, and 12 patients (15.4%) were diagnosed with pituitary metastases using pathologic and/or MRI criteria. Of the 21 patients with prior cancer diagnosis, 52.4% were diagnosed with pituitary metastases: 28.6% using MRI criteria and 23.8% using pathologic criteria. Average age of patients with metastases was 61.8 years. Tumor pathology consisted of 33.3% breast, 33.3% lung, 8.3% esophageal, 8.3% renal, 8.3% neuroendocrine and 8.3% melanoma. Pituitary metastasis diagnosis led to one patient's initial cancer diagnosis. Symptoms at diagnosis included 33.3% headaches, 41.7% endocrinopathies, and 25% visual deficits. Treatment included surgical intervention plus radiation in 41.7%, surgery alone in 8.3%, radiation alone in 25%, and observation alone in 25%. Median follow-up, progression-free-survival, and overall survival was 8.8 months, 4.5 months, and 11.5 months, respectively. Incidence of pituitary metastases in our cohort is higher than previously reported in the general population. Given these findings, there may be a role for early excisional biopsy or resection of sellar/suprasellar lesions in cancer patients, as confirmation of CNS metastatic disease may require targeted brain radiation and/or alteration of systemic therapy.

Keywords: Pituitary Metastases, Cancer Patients, Clinical Outcomes

1. Introduction

Pituitary metastases have long been considered rare complications of malignancy. The prevalence of pituitary metastases ranges from 0.4% to 5% in radiological and surgical studies [1-3]. Prior studies have alluded to the increasing prevalence of pituitary metastases [4-8]. This may reflect improved imaging modalities, increasing surveillance, or increasing survival from primary systemic disease.

Metastasis to the pituitary gland and sellar/suprasellar region occurs either through direct extension or via venous or arterial spread [9]. The most common primary malignancies that spread to the pituitary gland are lung and breast malignancies [4, 6, 9, 10]. The most common symptoms at diagnosis include visual deficits, headache, cranial nerve palsy, and polyuria and polydipsia suggestive of diabetes insipidus [4].

Traditional treatment for benign pituitary lesions entails conservative management with serial imaging, with surgery

reserved for more symptomatic lesions, macro-adenomas or those demonstrating rapid growth. However, treatment for pituitary metastases may require excisional biopsy or resection for pathologic confirmation; to help guide radiation and/or systemic therapy. The prevalence of pituitary metastases among cancer patients are not clearly defined [4-8]. If the prevalence is higher than previously reported, there may be a role for early surgical intervention if pathology is needed to guide systemic or adjuvant therapies. The primary objective of this study to determine the incidence of pituitary metastases in our cohort and secondarily to report our outcomes.

2. Methods

Following IRB approval, we conducted a single-center, retrospective chart review of patients undergoing neurosurgical evaluation for sellar/suprasellar lesions discovered on magnetic resonance imaging from 2008-2020 at Moffitt Cancer Center, a National Cancer Institute-designated Comprehensive Cancer Center. Demographic data, presenting symptoms, radiographic features, interventions, and outcomes were collected and analyzed. Primary inclusion criterion included patients with a pathologically confirmed or radiologically suspected pituitary metastasis. Primary exclusion criterion included any non-metastatic pituitary lesion.

3. Data Collection

A literature review was performed and used in the development of our data collection tables [4-8, 11] which included demographic data, signs and symptoms at presentation, radiographic features of the sellar/suprasellar lesion, and outcomes data. Demographic data included age at diagnosis of the pituitary metastasis, gender, pituitary metastasis pathology, years between primary cancer and pituitary metastasis diagnosis, other intracranial metastasis at the time of pituitary metastasis diagnosis, and if the patient was on systemic treatment at the time of pituitary metastasis diagnosis. Signs and symptoms at presentation were recorded. Radiographic data included the reason why the magnetic resonance imaging study that diagnosed the pituitary metastasis was initially obtained, location of the metastasis, cavernous sinus involvement, suprasellar extension, optic nerve compression, and radiographic growth from prior imaging. Outcomes data were assessed by investigating primary and secondary treatment modalities, surgical approach, extent of resection, radiation regimen, last known follow-up, progression-free-survival from primary treatment of the pituitary metastasis, mortality, and overall survival from time of pituitary metastasis diagnosis.

4. Results

We reviewed 78 consecutive patients presenting to the neurosurgical oncology practice for evaluation of a pituitary lesion. 12 patients (15.4%) met the inclusion criterion of having a pituitary metastasis diagnosed using pathologic

and/or MRI criteria, while 66 patients were excluded for having non-metastatic lesions. 21 patients (26.9%) of the 78 patient charts reviewed had a prior cancer diagnosis, and 11 of the 12 patients with pituitary metastasis had a prior cancer diagnosis. Of the 21 patients with prior cancer diagnosis, 11 patients (52.4%) were diagnosed with pituitary metastasis; 6 of 21 patients (28.6%) using MRI criteria and 5 of 21 patients (23.8%) pathologic criteria. Of the 12 patients who met the inclusion criterion of having a pathologically confirmed or radiologically suspected pituitary metastasis; 58.3% were female and 41.7% were male. The average age of patients at pituitary metastasis diagnosis was 61.8 years old. Primary cancer pathology consisted of 4 patients (33%) with breast cancer, 4 patients (33.3%) with lung cancer, 1 patient (8.3%) with esophageal cancer, 1 patient (8.3%) with clear cell renal carcinoma, 1 patient (8.3%) with neuroendocrine carcinoma and 1 patient (8.3%) with BRAF mutant melanoma. The pituitary pathology of patients with breast cancer metastases included 2 patients with ER+/PR-/HER2+, 1 patient with ER+/PR-/HER2-, and 1 patient with ER+/PR+/HER2- breast cancer. Of the patients with lung cancer pituitary metastases, 1 patient had squamous cell carcinoma of the lung without *EGFR* or *Alk* mutation, 1 had a carcinoid tumor of the lung without *EGFR* or *Alk* mutations, 1 had poorly differentiated adenocarcinoma of the lung, and 1 had small cell carcinoma of the lung. 11 patients (91.7%) had prior history of a primary cancer, while for 1 patient (8.3%) the pituitary metastasis provided the initial tissue that led to the patient's initial cancer diagnosis. The time between primary cancer and pituitary metastasis diagnosis ranged from 0 to 6 years for this cohort, with 8 patients (66.7%) being diagnosed with a pituitary metastasis in the first 2 years of their cancer diagnosis. 5 patients (41.7%) had other intracranial metastasis at the time of pituitary metastasis diagnosis and 8 patients (66.7%) had already undergone systemic treatment for the primary cancer at the time of pituitary metastasis diagnosis (Table 1). With regards to signs and symptoms at presentation, 4 patients (33.3%) presented with headaches, 5 patients (41.7%) presented with endocrinopathies, and 3 patients (25%) presented with visual deficits (Table 2). Of the patients with endocrinopathies, 2 had cortisol and thyroid hormone abnormalities, 1 had diabetes insipidus, 1 had panhypopituitarism, and 1 had testosterone abnormalities.

Six patients (50%) had magnetic resonance imaging that identified their pituitary metastasis on follow-up or staging imaging, while the other 6 patients (50%) had symptoms that led providers to obtain imaging. Follow-up imaging consisted of follow-up of known asymptomatic pituitary lesion or follow-up of other intracranial lesions or metastases, as 5 patients had other intracranial metastases at the time of pituitary metastasis diagnosis. With regards to radiographic features of the pituitary metastases, 75% involved the anterior pituitary gland, 16.7% involved the posterior gland, and 58.3% involved the infundibulum (Table 3). 58.3% extended into the suprasellar region, 33.3% had cavernous sinus involvement and 33.3% had optic nerve compression. 66.7% had radiographic growth compared to prior imaging.

Initial treatment in our cohort consisted of surgical intervention and radiation in 5 patients (41.7%), surgery alone in 1 patient (8.3%), radiation alone in 4 patients (25%), and observation alone in 4 patients (25%). Of patients undergoing surgery, the primary approach was endoscopic endonasal with 1 patient also requiring craniotomy. Subtotal resection with significant cytoreduction was achieved in all surgical cases. Adjuvant fractionated radiotherapy was provided to 5 out of the 6 surgical patients, with 1 patient passing away prior to initiation of fractionated radiotherapy.

Secondary treatment for tumor re-growth was carried out in 3 patients (25%) and consisted of re-resection and re-irradiation in 2 patients and re-irradiation alone in 1 patient (Table 4). Mean follow-up for our cohort was 15.9 months, with a median of 8.8 months and a range of 0.7 to 57.9 months. Mean progression-free-survival from initial diagnosis of pituitary metastasis was 12.9 months, with a median of 4.5 months and a range of 0 to 43 months. Lastly, mean overall survival was 17.8 months, with a median of 11.5 months and a range of 0 to 57 months (Table 5).

Table 1. Demographic Data for Patients with Pituitary Metastasis.

Patient ID #	PM Pathology	PM leading to initial cancer diagnosis	Years between primary cancer & PM diagnosis	Intracranial metastasis at time of PM diagnosis	Systemic treatment at time of PM diagnosis
24	Clear Cell Renal	Y	0	Y	N
28	Esophageal	N	0	N	N
38	ER+/PR-/HER2+ Breast	N	6	N	Y
47	Squamous Cell Ca of the Lung	N	4	N	N
53	ER+/PR-/HER2-Breast	N	5	N	Y
55	Neuroendocrine	N	1	N	Y
56	Small Cell Lung	N	0	Y	Y
58	ER+/PR+/HER2-Breast	N	2	N	Y
59	ER+/PR-/HER2+ Breast	N	5	Y	Y
61	BRAF mutant Melanoma	N	0	Y	Y
62	Adenocarcinoma of the Lung	N	0	N	Y
69	Carcinoid tumor of the Lung	N	2	Y	N

ID #, identification number; NSCLC, non-small cell lung cancer; PM, pituitary metastasis

Table 2. Signs and Symptoms at Presentation.

Patient ID #	Headaches	Endocrinopathy	Visual Deficits
24	Y	N	Y
28	Y	N	Y
38	N	Y	N
47	N	Y	N
53	Y	N	Y
55	N	N	N
56	N	N	N
58	N	Y	N
59	N	Y	N
61	N	N	N
62	Y	N	N
69	N	Y	N

ID #, identification number

Table 3. Radiographic features of pituitary metastases.

Patient ID #	Reason MRI Diagnosing PM Was Obtained	Location	Cavernous Sinus Involvement	Suprasellar Extension	Optic Nerve Compression	Radiographic Growth
24	Chemosis Proptosis	Anterior Pituitary / Infundibulum	Y	Y	Y	Y
28	Headaches Vision loss	Anterior/Posterior Pituitary	Y	Y	Y	Unknown
38	Nausea Vomiting Systemic disease progression	Anterior Pituitary / Infundibulum	N	N	N	Y
47	Hyponatremia	Anterior Pituitary / Infundibulum	Y	N	N	Y
53	Headaches Vision loss	Anterior Pituitary	Y	Y	Y	Y
55	Follow-up	Hypothalamus / Infundibulum	N	Y	Y	Y
56	Staging	Anterior Pituitary / Infundibulum	N	N	N	Unknown
58	Staging	Anterior Pituitary / Infundibulum	N	Y	N	N
59	Follow-up	Anterior Pituitary	N	Y	N	Y
61	Follow-up	Infundibulum	N	Y	N	Y
62	Headaches	Posterior Pituitary	N	N	N	Unknown
69	Follow-up	Anterior Pituitary	N	N	N	Y

ID #, identification number; N, no; Y, yes

Table 4. Treatment Paradigms.

Patient ID #	First Treatment	Surgical approach	EOR	Radiation timing	Radiation dose	Second Treatment
24	Surgery + Radiation	eTSS + craniotomy	STR	Adjuvant	25 Gy / 5 fx	30Gy in 5 fractions
28	Surgery + Radiation	eTSS	STR	Adjuvant	48 Gy / 24 fx	Re-resection + re- irradiation
38	Surgery + Radiation	eTSS	STR	Adjuvant	25 Gy / 5 fx	Re-resection + re-irradiation
47	Surgery	eTSS	STR	Planned FSRT but mortality prior to treatment	None	None
53	Surgery + Radiation	eTSS	STR	Adjuvant	OSH Fractionated RT	Lost to follow-up
55	Radiation	N/A	N/A	Primary	30 Gy / 10 fx	Lost to follow-up
56	Observation	N/A	N/A	Planned WBRT as outpatient	None	None- opted for hospice
58	Observation	N/A	N/A	N/A	N/A	None
59	Radiation	N/A	N/A	Primary	25 Gy / 5 fx	None
61	Observation	N/A	N/A	N/A	N/A	None
62	Radiation	N/A	N/A	Primary	30 Gy / 10 fx (only 5 fx completed)	None- opted for hospice
69	Surgery + Radiation	eTSS	STR	Adjuvant	OSH Fractionated RT	None

EOR, extent of resection; eTSS, endoscopic transsphenoidal surgery; FSRT, fractionated stereotactic radiotherapy, fx, fractions; Gy, gray; ID #, identification number; LKFU, last known follow-up from time from diagnosis of pituitary lesion to last clinical documentation available in chart; N/A, not applicable; OS, overall survival from time from radiographic diagnosis of pituitary lesion to death (if mortality) or last known follow-up; OSH, outside hospital; PFS, progression free survival (Time from intervention or first scan if only observed to documented progression); STR, subtotal resection; WBRT, whole brain radiotherapy

Table 5. Outcomes.

Patient ID #	LKFU (days)	PFS (months)	Mortality Y/N	OS from PM Diagnosis (months)
24	1762	41	Y	57
28	347	0	Y	9
38	844	6	Y	29
47	21	0	Y	0
53	120	Unknown	Y	14
55	392	13	Y	28
56	29	Unknown	Y	3
58	657	21	Y	21
59	187	3	Y	6
61	114	2	Y	3
62	27	0	Y	1
69	1315	43	N	43

ID #, identification number; LKFU, last known follow-up from time from diagnosis of pituitary lesion to last clinical documentation available in chart; OS, overall survival from time from radiographic diagnosis of pituitary lesion to death (if mortality) or last known follow-up; PFS, progression free survival (Time from intervention or first scan if only observed to documented progression); PM, pituitary metastasis; Y/N, yes/no.

5. Discussion

The incidence of pituitary metastases in our cohort is higher than previously reported in the general population. We found the incidence to be 15.4% in patients presenting for neurosurgical evaluation with abnormal pituitary magnetic resonance imaging; and ranging from 23.8% to 52.4% in patients with a prior cancer diagnosis. This incidence is higher than the previously reported prevalence of 0.4-5% among the general population [1-3]. Many studies to date have focused on case presentations, outcomes, and survival analyses among all-comers without focus on subgroups or disease prevalence [3-5, 7, 8, 10-17]. Identifying this increased incidence of pituitary metastases among cancer patients in our cohort is a subtle but significant distinction and may serve to more accurately direct patient care in the setting of progressive systemic disease. Given the increased incidence in this subgroup, there may be a role for early excisional biopsy or resection of sellar/suprasellar lesions in cancer patients. Over half (6/11) of our patients did not have

prior or concurrent CNS disease, thus the confirmation of CNS metastatic disease to the pituitary prompted targeted brain radiation and/or alteration of systemic therapy.

Like prior studies, lung and breast cancer pathology were the most common among pituitary metastases in our study [4, 5, 8, 10]. This may reflect a higher prevalence of these diseases rather than a predilection for these to spread to the sellar/suprasellar region. Unlike the study by Patel et al, our cohort had less signs and symptoms at presentation with 41.7% having some endocrinopathy, 33.3% presenting with headaches and 25% with visual deficits; this contrasts their findings of 70% having pituitary insufficiency, 47% having headaches, and 62% having visual deficits [4]. A potential explanation for why patients in our cohort were less symptomatic may be due to the high level of surveillance and follow-up that occurs at our multidisciplinary cancer center which may contribute to patients presenting earlier and while still asymptomatic. This may also account for why two thirds of our cohort had radiographically proven growth from prior imaging and only one third of our cohort had optic nerve compression. Alternatively, more frequent, or lower

thresholds for hormonal screening labs may help detect earlier signs of endocrine dysfunction. Similar to the study by Marin et al [18] there was a slight preponderance of metastases to the anterior gland in our cohort, but a histological study by Kleinschmidt-Demasters et al showed equal metastatic involvement to the posterior pituitary gland as well [19].

A study of pituitary metastases and MRI findings by Mayr et al reported that pituitary metastases in their series were relatively small and seen as enhancing pituitary lesions (less than or equal to 1.5 cm) that were relatively isointense to brain on both T1- and T2- weighted non-contrast images (78%) and involved the hypothalamus/pituitary infundibulum (44%) or cavernous sinus (56%) [13]. These findings are consistent with the differentiating features of pituitary metastases in our series. Pituitary metastases typically enhance after contrast administration and were seen as hyperintense lesions on post-contrast T1 weighted images while pituitary adenomas enhance less than normal pituitary tissue on both routine and dynamic contrast enhanced pituitary imaging. Pituitary adenomas tend to be more sharply margined compared to metastases. Both adenomas and metastases can demonstrate hyperintense signal on non-contrast T1- weighted imaging from the paramagnetic effect of hemorrhage or melanin. Immunotherapy-induced hypophysitis has become a well-known adverse effect related to immune checkpoint inhibitor therapy and is difficult to differentiate from metastasis on a single or initial MRI exam, often having imaging findings similar to metastatic disease. Hypophysitis typically results in diffuse enlargement and enhancement of the gland and infundibulum. We find that the best tool in differentiating between these two pathologies include serial imaging and close follow-up given that hypophysitis tends to improve whereas a pituitary metastasis that have escaped systemic therapy would likely progress. Hypophysitis more commonly involves the infundibulum on the initial MRI examination whereas metastases are more commonly seen in the pituitary gland.

The outcomes of our study showed a similar median overall survival from pituitary metastasis detection to a study by Lithgow et al, who reported a median survival of 11 months with a range of 2 to 47 months. However, other studies by Habu et al, Patel et al, and Ng et al reported a median survival time of 12.9 months, 13.3 months, and 14 months, respectively [4, 8, 11]. One factor contributing to our decreased median survival time compared to those studies may be related to the fact that only 50% of our cohort underwent surgery, as dictated by patient condition, multiple medical comorbidities, and patient wishes. Although study findings vary with regards to the benefits of surgery [11], Patel et al. found surgical resection to be associated with longer overall survival and reported that the 18 patients in their cohort who underwent surgery had a median overall survival after resection of 48.6 months [4]. The large percentage of non-operative intervention in our cohort may have contributed to our cohort's slight decrease in median survival compared to others. Similar to others, our practice

during the study period was to surgically intervene for large symptomatic metastases causing optic nerve compression or those demonstrating rapid interval growth. Thus, earlier surgical intervention may have potentially improved survival. Lastly, our study spans a broad time period, during which there have been many advances in targeted and immunotherapies making it impossible to ascribe outcomes data to any one particular intervention with this study design.

Evaluating the efficacy of treatment paradigms was beyond the scope of this study. We present our patients' treatment paradigms to illustrate the individuality and details involving each patient's care. It emphasizes the ever changing landscape for treatment of brain metastasis. It also highlights the importance and need for additional prospective studies to determine if earlier diagnosis and standardization of intervention can benefit this population.

6. Limitations

Limitations of this study include small cohort size, inherent biases associated with retrospective chart reviews, as well as lack of generalizability of our cohort's results to cancer patients without sellar/suprasellar lesions on magnetic resonance imaging or the general population. Similar to other studies in the literature, another limitation is the combination of both pathology confirmed and radiology suspected patients within this cohort. In attempts to mitigate this limitation, we only included radiological pituitary metastases that had characteristics of pituitary metastases as determined by our dedicated neuroradiologists. Lastly, we report the incidence of pituitary metastases in our cohort, but this is not to serve as a prevalence study; a cross-sectional study would best serve to identify the true prevalence of pituitary metastases. However, obtaining magnetic resonance imaging across an entire cancer population would exert a financial strain on the health care system. Therefore, extrapolation of data from cohort studies such as ours may be the best way to assess increasing prevalence of pituitary metastases. Larger studies combining all patients presenting for evaluation of pituitary lesions to the departments of radiation-oncology, endocrinology, and neurosurgery will need to be conducted in the future to more accurately investigate the prevalence of pituitary metastases among broader populations.

7. Conclusion

The incidence of pituitary metastases in our cohort is higher than previously reported in the general population. Given these findings, there may be a role for early excisional biopsy or resection of sellar/suprasellar lesions in cancer patients; as confirmation of CNS metastatic disease may require targeted brain radiation and/or alteration of systemic therapy.

Submission Statement

This manuscript is original and has not been submitted

elsewhere in part or in whole.

Data Availability Statement

Data are available on reasonable request. De-identified data are available on reasonable request.

Ethics Statements

Patient consent for publication not required.

Ethics Approval

This study was approved by Moffitt Cancer Center IRB under protocol number MCC 18297.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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