

# Prognostic Factors in Cancer Patients with Symptomatic Pituitary Metastasis: A Clinical Case Study

CHUN-YU LIN<sup>1</sup>, WEN-KUAN HUANG<sup>2</sup>, FU-TSAI CHUNG<sup>1</sup> and HSIEN-KUN CHANG<sup>2</sup>

*Divisions of <sup>1</sup>Pulmonary and Critical Care Medicine and <sup>2</sup>Hematology-Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan, R.O.C.*

**Abstract.** *Background/Aim: Pituitary metastasis has a rare and indolent course that impedes early diagnosis and treatment. Nevertheless, local tumor control may improve survival. However, few studies provide information regarding the prognosis of patients with pituitary metastases. We aimed to determine these prognostic factors. Patients and Methods: We retrospectively reviewed clinical presentation, diagnosis and management of patients with pituitary metastases. Data were collected at a single Institution between January 1990 and March 2013 and the prognostic factors were analyzed. Results: Eighteen patients with symptomatic pituitary metastasis were reviewed. The median survival was 4.1 months after the diagnosis of pituitary metastasis. Solitary pituitary metastasis and good performance status (Eastern Cooperative Oncology Group (ECOG) score  $\leq 2$ ) had prognostic value but not age, gender or primary tumor type. Patients receiving local therapy for pituitary metastasis had significantly longer survival (6.52 versus 0.9 months,  $p=0.0143$ ), regardless of ECOG status (16.9 versus 4.3 months,  $p=0.09$  in ECOG  $\leq 2$ ; 2.7 versus 0.8 months,  $p=0.08$  in ECOG  $>2$ ). Conclusion: Despite the dismal prognosis of patients with pituitary metastases, having a solitary pituitary metastasis, good performance status and receiving local therapy can prolong survival.*

Pituitary metastasis in cancer patients is a devastating complication of malignancy and has a poor prognosis. Previous studies of autopsy series reported pituitary metastasis in 0.14-28.1% of all brain metastases (1, 2). Pituitary metastases are commonly diagnosed in lung and

breast cancer cases. The increasing frequency of diagnosis can be attributed to improved survival of cancer patients and improved imaging techniques (2).

Only 8% of patients who have pituitary metastases develop pituitary-related symptoms (2, 3). The most frequent symptom is central diabetes insipidus, resulting from posterior lobe or stalk involvement (4) indicating that metastasis to the posterior pituitary gland is more common than to the anterior lobe. In certain case reports, pituitary dysfunction is the first presentation of occult primary tumor and the only site of metastasis (3, 5-8). Pituitary metastases are difficult to diagnose because the symptoms overlap with other complicated disorders often seen in patients with advanced cancer. Moreover, pituitary metastases are usually too small to cause radiological changes and difficult to differentiate from other benign neoplasms using the imaging techniques available (9).

Morital *et al.* showed that local control of pituitary metastasis, including surgical decompression and radiation therapy, was associated with significant improvement in survival and improved the quality of life in patients diagnosed with symptomatic pituitary metastasis (3). Some case series reported that stereotactic radiosurgery is a minimally-invasive outpatient management option for the treatment of brain metastases (3, 4, 10-12). The median survival after intervention and treatment for pituitary metastasis ranged from 5.2 to 10 months but none of these studies discussed the prognostic factors.

Herein, we retrospectively reviewed the medical records of 18 cancer patients who had pituitary metastases and analyzed the prognostic factors in these patients.

## Patients and Methods

**Study population.** We studied 18 patients who had symptomatic pituitary metastasis and were registered in a single Institution between January 1990 and March 2013. Medical records were reviewed to retrieve their history, radiology and pathology reports, treatment and outcome. This retrospective study was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (CGMH 101-5180B).

*Correspondence to:* Dr. Hsien-Kun Chang, Division of Hematology-Oncology, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan Township, Taoyuan County 333, Taiwan (R.O.C.). Tel: +886 33281200 (ext. 8825), Fax: +886 33281200 (ext. 2362), e-mail: chk0329@seed.net.tw

**Key Words:** Prognosis, pituitary metastasis.

Table I. Clinical characteristics, treatment after pituitary metastasis and outcome.

Case No.	PS	Age/Gender	Primary cancer	Local therapy for pituitary metastasis	Systemic treatment for primary cancer	Survival after pituitary metastasis (months)
1	1	47/M	Lung adenocarcinoma	*Surgery		14.8
2	3	72/M	Lung adenocarcinoma	None		1.0
3	2	57/M	Lung adenocarcinoma	*Surgery, WBRT	Iressa	17.6
4	4	51/F	Lung adenocarcinoma	WBRT		0.7
5	2	73/M	Lung adenocarcinoma	WBRT	CT	9.7
6	1	64/M	Lung SCC	*Surgery	CT	3.9
7	1	52/M	Lung SCC	Local RT	CT, Tarceva	14.3
8	4	30/F	Breast	WBRT		2.3
9	4	57/F	Breast	None		0.8
10	2	58/F	Breast	Local RT	CT	29.3
11	4	44/F	Breast	WBRT	Tamoxifen	5.33
12	4	47/F	Breast	WBRT	Herceptin	0.8
13	2	82/M	Unknown primary	None		4.3
14	2	56/M	Lymphoma	WBRT	IT, CT	19.6
15	3	69/F	Lymphoma	*Surgery	CT	7.7
16	2	63/F	Lymphoma	*Surgery	IT	2.43
17	4	63/F	Leiomyosarcoma	None		0.45
18	4	38/M	Germinoma	CCRT for the brain		3.0

F, Female; M, male; PS, performance status; CDI, central diabetes insipidus; CT, chemotherapy; RT, radiotherapy; WBRT, whole brain radiotherapy; CCRT, concurrent chemoradiotherapy; IT, intrathecal chemotherapy; SCC, squamous cell carcinoma; \*Surgery, endoscopic transsphenoidal surgery or craniotomy.

**Diagnosis of pituitary metastasis and symptoms.** The diagnosis of pituitary metastasis was obtained by using brain imaging studies, including computed tomography (CT) and/or magnetic resonance imaging (MRI). The symptoms of pituitary metastasis are pituitary dysfunction, such as central diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), adrenal insufficiency or hypothyroidism.

**Modalities of local pituitary therapy.** Local pituitary therapy included surgical intervention, local radiation for pituitary tumors or whole-brain radiotherapy.

**Statistical analysis.** Survival was estimated by Kaplan-Meier analysis. We performed a univariate analysis using the log-rank test to assess factors that might influence overall survival. The following variables were assessed: gender, cancer stage, solitary pituitary or multiple brain metastases and the primary cancer type. All statistics were calculated by using the Prism software, version 5 (GraphPad Software Inc., La Jolla, CA, USA). Differences were considered significant at  $p \leq 0.05$  (two-tailed).

**Results**

Out of the 18 patients with metastatic pituitary tumors, 7 had lung cancer, 5 female patients had breast cancer and 3 cases were malignant lymphoma. There were 9 men and 9 women with a median age of 56.8 years (range=30-82 years). Five patients received surgery, including endoscopic transsphenoidal surgery or craniotomy, one of whom followed-up with whole-brain radiotherapy after surgery. Seven patients received whole-brain radiotherapy, while 3

received localized radiotherapy to the pituitary region (Table I). Eleven patients presented with central diabetes insipidus, 5 had limited eye motility, 4 complained of having vague headaches and 2 reported visual-field defects. Nine patients had solitary pituitary metastasis and 9 developed multiple brain metastases (Table II). Patients' characteristics, including gender, the primary cancer type, performance status, solitary pituitary or multiple brain metastases and the use of local therapy for pituitary metastasis and its impact on survival, are shown in Table III.

The median overall survival was 4.1 months after diagnosis of pituitary metastasis (range=0.45-29.3 months). There was no difference in the median survival by comparing the gender or the primary cancer type. Patients who had a solitary pituitary metastasis demonstrated better survival than those who had multiple brain metastases, although this difference did not reach statistical significance (7.7 versus 1.0 months, hazard ratio (HR)=0.36, 95% confidence interval (CI)=0.12-1.03,  $p=0.055$ ) (Figure 1). Longer survival were observed in patients who received local therapy for pituitary metastasis (6.52 versus 0.9 months, HR=0.10, 95% CI=0.02-0.63,  $p=0.0143$ ) (Figure 2). Patients who had a good performance status (Eastern Cooperative Oncology Group (ECOG) score  $\leq 2$ ) also had longer survival (14.3 versus 1.0 months, HR=0.12, 95% CI=0.03-0.42,  $p=0.0009$ ) (Figure 3). In subgroup analysis, the patients who received local therapy for pituitary metastasis demonstrated better survival in both ECOG  $\leq 2$  and ECOG  $>2$  groups, although this did not reach

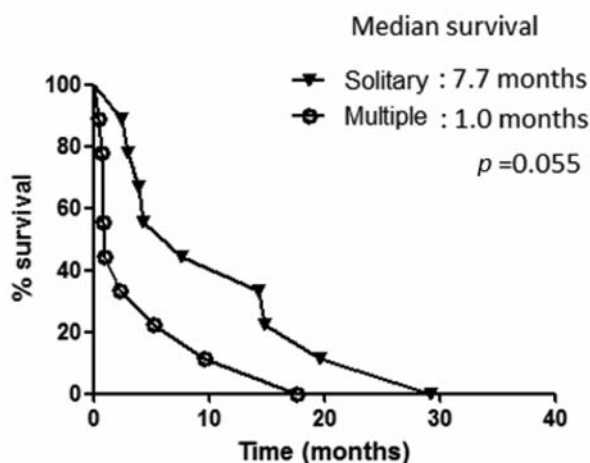


Figure 1. Patients with a solitary pituitary metastasis demonstrated better median survival than those with multiple brain metastases (7.7 months vs. 1.0 month, log-rank test, hazard ratio (HR)=0.36, 95% confidence interval (CI)=0.12-1.03,  $p=0.055$ ).

Table II. Clinical presentation of pituitary metastasis (Total No.=18).

	No. (%)
Symptoms	
Central diabetes insipidus	11 (61.1%)
Eye motility limitation	5 (27.8%)
Vague headache	4 (22.2%)
Visual field defect	2 (11.1%)
Endocrine abnormality	
Panhypopituitarism	9 (50%)
Central diabetes insipidus	7 (38.9%)
Anterior pituitary dysfunction	2 (11.1%)
SIADH	1 (5.5%)
Brain metastases	
Solitary pituitary metastasis	9 (50%)
Pituitary with multiple brain metastases	9 (50%)

SIADH, Syndrome of inappropriate anti-diuretic hormone secretion.

statistical significance either (16.9 *versus* 4.3 months,  $p=0.09$ ; 2.7 *versus* 0.8 months,  $p=0.08$ , respectively) (Table III).

There were no intolerable adverse effects or complications resulting from the local therapy for pituitary metastasis.

## Discussion

Given the rare incidence and difficulty of diagnosing pituitary metastases, only a few cases have been reported in the literature. To our knowledge, ours is the first study to examine prognostic factors in pituitary metastases. In our opinion, local therapy for pituitary metastasis and a good

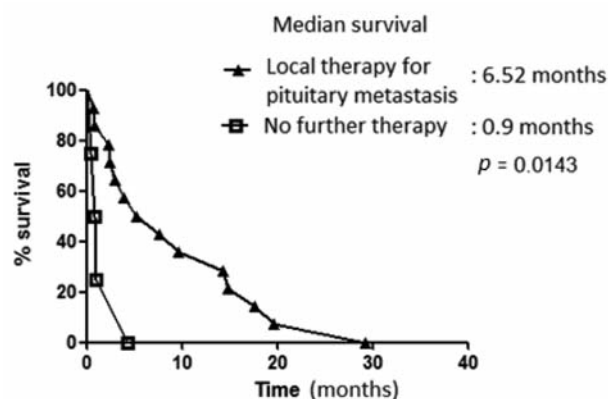


Figure 2. Patients receiving local therapy for pituitary metastasis had significantly longer median survival (6.52 months vs. 0.9 months, log-rank test, hazard ratio (HR)=0.10, 95% confidence interval (CI)=0.02-0.63,  $p=0.0143$ ).

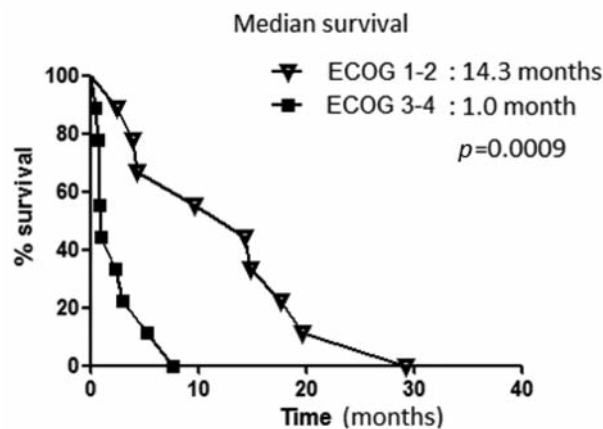


Figure 3. Patients with a good performance status (ECOG score  $\leq 2$ ) had longer median survival (14.3 vs. 1.0 months, hazard ratio (HR)=0.12, 95% confidence interval (CI)=0.03-0.42,  $p=0.0009$ ).

performance status had a significant impact on patient survival. Indeed, local therapy may play an important role in patient survival in spite of the performance status. For instance, in both ECOG  $\leq 2$  and ECOG  $> 2$  groups, we observed a trend toward superior outcomes in patients receiving local therapy for pituitary metastasis.

Central diabetes insipidus is the most frequent presentation of pituitary metastasis (3, 4, 6, 7). This clinical manifestation correlated to pituitary metastases that mainly developed in the posterior lobe (2-4, 8). Four pathways of metastatic spread to the pituitary have been identified: (i) direct blood-borne metastasis to the posterior lobe, (ii) blood borne metastasis *via* the hypothalamus-hypophyseal portal system or the *infundibulum*, (iii) extension from the

Table III. Sub-group analysis of survival.

	No.	Survival (months)	p-Value	95% CI
Median survival after pituitary metastasis	18	4.1		
Gender				
Male	9	9.7	0.28	0.2-1.6
Female	9	2.3		
Primary cancer type		0.09		
Lung	7	9.7		
Breast	5	2.3		
Others	6	3.7		
Brain metastases			0.055	0.12-1.03
Solitary pituitary metastasis	9	7.7		
Pituitary with multiple brain metastases	9	1.0		
Performance status			*0.0009	0.03-0.4
ECOG ≤2	9	14.3		
ECOG >2	9	1.0		
Local therapy for pituitary metastasis			*0.0143	0.02-0.63
Yes	14	6.5		
No	4	0.9		
Local therapy in ECOG ≤2			0.09	0.00034-1.87
Yes	8	16.9		
No	1	4.3		
Local therapy in ECOG >2			0.08	0.021-1.28
Yes	6	2.7		
No	3	0.8		

ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; \*Statistically significant.

juxtaseilar region and skull-base metastasis and (iv) leptomeningeal spread with involvement of the pituitary capsule through the suprasellar cistern (2-4). Pituitary metastases are difficult to discern because of their complex presentations and non-specific radiological changes. The definitive diagnosis of pituitary metastasis requires a tumor biopsy and pathology testing. However, because of the high risk of surgical intervention for sellar lesions and the poor performance status in terminal cancer patients, tissue proofs are not always available. As the posterior pituitary lobe is a preferential site for metastasis and the tumor-invasive characteristics are known, as summarized by Ribal *et al.*, a clinical evaluation can differentiate malignant from benign adenoma. Symptoms, such as central diabetes insipidus, abnormal eye motility or visual deficit and vague headaches, all highly suggest the presence of pituitary metastatic lesions. Central diabetes insipidus and abnormal eye motility both have independent predictive values when analyzed using multivariate regression analysis. The combination of all four symptoms above had the greatest predictive value for pituitary metastases (13). This finding is quite useful in clinical practice. Our study had similar findings showing that central diabetes insipidus is the most frequent and specific presentation.

The purpose of treatment for pituitary metastases was usually palliative (*i.e.*, to improve the quality of life and

delay the disease progression). Symptomatic control using pituitary hormone substitution therapy was widely found to result in good responses. Still, recent studies show that local therapy for pituitary metastasis is warranted. However, because of the abundant vascularity of the pituitary area, total removal of the metastatic tumor is not feasible. Indeed, as an alternative, whole-brain or local radiotherapy was traditionally applied as palliative treatment for pituitary metastases. In most studies, the local palliative treatment for pituitary metastases showed an improvement in the quality of life but not in survival (2, 10, 14). Morita *et al.* demonstrated an improvement in survival when local tumor control was achieved by multi-modality treatments, such as surgery, radiation or chemotherapy (3). A few case reports also demonstrated that pituitary metastatic tumor resection in combination with whole-brain radiotherapy can significantly prolong survival (14, 15). However, the lack of information regarding performance status, a well-known independent prognostic factor, may bias the results from the survival analysis. Our case study shows that there was no survival difference based on gender or the primary cancer type. Several factors significantly influenced the outcome, including local therapy for pituitary metastasis, good performance status (ECOG ≤2) and possibly solitary pituitary metastasis. There were no intolerable adverse effects or complications reported in the group undergoing

local therapy for pituitary metastasis. These results suggest that local therapy, such as surgery and whole-brain or local radiotherapy for pituitary metastasis, can be considered even in patients who have poor performance status.

Our study had some limitations. Firstly, this study was performed on a small number of patients. Although a significantly favorable outcome was found in the patient groups that underwent local therapy for pituitary metastasis or had a good performance status and solitary pituitary metastasis, a larger prospective study is warranted in order to confirm our findings. Secondly, we retrospectively enrolled patients who visited the institution between 1990 and 2013. As such, the follow-up regarding the patients' quality of life after local therapy was not comprehensively recorded and evaluated.

Early detection of pituitary metastasis, followed by adequate local treatment, may improve survival and the quality of life. In cancer patients presenting with polyuria and/or polydipsia, we should be mindful of central diabetes insipidus as a differential diagnosis with hyperglycemia or hypercalcemia. Nevertheless, the presence of these symptoms, along with visual field deficit, abnormal eye motility and vague headaches, highly suggest pituitary metastasis. In conclusion, our study shows that patients with solitary pituitary metastasis, good performance status and receiving local therapy for pituitary metastasis demonstrated better survival. Local therapy for pituitary metastasis may have a survival benefit in spite of a patient's performance status. Larger prospective studies are warranted in order to confirm our findings.

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