Pituitary metastases: current practice in Japan

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OBJECT With advancement of cancer treatment and development of neuroimaging techniques, contemporary clinical pictures of pituitary metastases (PMs) must have changed from past reports. The goal of this paper was to elucidate the clinical features of PMs and current clinical practice related to those lesions. In this retrospective study, questionnaires were sent to 87 physicians who had treated PMs in Japan.

RESULTS Between 1995 and 2010, 201 patients with PMs were treated by the participating physicians. The diagnosis of PM was histologically verified in 69 patients (34.3%). In the other 132 patients (65.7%), the PM was diagnosed by their physicians based on neuroimaging findings and clinical courses. The most frequent primary tumor was lung (36.8%), followed by breast (22.9%) and kidney (7.0%) cancer. The average interval between diagnosis of primary cancer and detection of PM was 2.8 ± 3.9 (SD) years. Major symptoms at diagnosis were visual disturbance in 30.3%, diabetes insipidus in 27.4%, fatigue in 25.4%, headache in 20.4%, and double vision in 17.4%. Major neuroimaging features were mass lesion in the pituitary stalk (63.3%), constriction of tumor at the diaphragmatic hiatus (44.7%), hypothalamic mass lesion (17.4%), and hyperintensity in the optic tract (11.4%). Surgical treatment was performed in 26.9% of patients, and 74.6% had radiation therapy; 80.0% of patients who underwent radiotherapy had stereotactic radiotherapy. The median survival time was 12.9 months in total. Contributing factors for good prognosis calculated by Cox proportional hazard analysis were younger age, late metastasis to the pituitary gland, smaller PM size, and radiation therapy. The Kaplan-Meier survival was significantly better in patients with breast cancer and renal cell cancer than in those with lung cancer.

CONCLUSIONS At the time of this writing, approximately 60% (120/201) of PMs had been treated by stereotactic radiation therapy in Japan. The median survival time was much longer than that reported in past series. To confirm the changes of clinical features and medical practice, a prospective and population-based survey is mandatory.

<http://thejns.org/doi/abs/10.3171/2014.12.JNS14870>

KEY WORDS pituitary metastasis; MRI; symptom; survival time; prognostic factor; oncology

ALTHOUGH malignant tumors metastasizing into the pituitary fossa are not infrequent events in autopsy series,^{6,10,17,18} pituitary metastasis (PM) is rarely diagnosed ante mortem.^{3,14,18} According to the Brain Tumor Registry of Japan, only 0.4% of intracranial metastatic tumors are located in the pituitary gland.⁵ These tumors account for only 1% of surgically treated pituitary tu-

mors.^{8,16,31} Recently, as the number of patients diagnosed with cancer has increased and their survival time has been extended, PMs have been diagnosed more frequently than before.^{16,20,24}

Many authors have reported their own experiences or their institutional series on PMs.^{3,11,13,14,20,26,31} There are also reviews involving large numbers of reported cas-

ABBREVIATION PM = pituitary metastasis.

SUBMITTED April 18, 2014. **ACCEPTED** December 30, 2014.

INCLUDE WHEN CITING Published online July 17, 2015; DOI: 10.3171/2014.12.JNS14870.

DISCLOSURE This study was financed by the National Cancer Center Research and Development Fund (grant no. 21-8-6: "Diagnosis and Treatment of Intractable Endocrine Tumors" by principal investigator, Dr. Akira Shimatsu) and supported by a Health and Labor Sciences Research grant on "Research on Intractable Diseases in Japan: Hypothalamo-Pituitary Dysfunction," and by a grant-in-aid (no. 20591716) awarded to Dr. Kazunori Arita from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the paper reported.

es.^{4,11,18,20,22,28} Accordingly, prognosis is generally poor, with a median survival time of around 6 months.^{4,11,18,20,22,27} However, these reports and reviews may have been biased from reports of infrequent clinical presentations of patients with this rare disorder¹⁶ and would be obsolete because some of the cases were treated 3–4 decades ago. Cancer treatments have recently been developing rapidly, and the prognosis for cancer patients has been improving (<http://ganjoho.jp/professional/statistics/>). Magnetic resonance imaging has facilitated the early detection of sellar lesions, and the diagnosis of PMs has been reported to largely depend on these imaging studies.^{13,14} Furthermore, recent reports have depicted cases of patients who survived long after the diagnosis.^{13,31} We should, therefore, consider the lack of a clear clinical picture of this disease in the era of MRI and advanced cancer treatment, which are essential for proper management of this disease. Therefore, we conducted a questionnaire study to elicit the diagnostic practice, clinical and radiological features, treatment modalities, and prognosis of PMs treated during a recent 15-year period in Japan.

Methods

Survey by Questionnaire

The first questionnaire simply asked about physicians' experiences with treating patients with PMs during a 15-year time period (1995–2010). The first questionnaire was sent by mail to all 365 clinics that have been designated as training centers for clinical endocrinology by the Japan Endocrine Society, which covers most endocrinology clinics in Japan, and to 860 members of The Japanese Society for Hypothalamic and Pituitary Tumors, representing a majority of centers treating hypothalamopituitary diseases in Japan. Considering the recent trend in Japan that general internists and surgeons treating cancers frequently send patients to stereotactic radiation centers without consulting neurosurgeons or endocrinologists when they find intracranial metastasis, the questionnaire was also sent to 56 stereotactic radiotherapy centers. The first questionnaire was distributed to 1069 physicians in 626 hospitals. Four hundred twenty-three (39.6%) physicians from 314 (50.2%) hospitals replied to the questionnaire; among them, 20.6% (87/423) from 84 hospitals reported that they had treated patients with PMs within the 15-year time span. Reports of 209 PMs were collected through the first questionnaire.

Subsequent questionnaires were sent to these 87 physicians to obtain detailed information, such as age, sex, primary tumors, symptoms, endocrinological status, MRI findings, treatment modalities such as surgery and radiotherapy, complications, and prognosis.

To determine the characteristics of extension of PMs, we compared geometric indicators on MRI of PMs with those of previously reported 50 cases of clinically non-functioning pituitary adenoma treated in Kagoshima University Hospital during 2007–2011.¹

Statistical Analyses

The Statflex version 6.0 software program (Artech Co.) was used for statistical analysis of the results. Depending on the characteristics of the data sets, data were analyzed

using Fisher's exact test, the Mann-Whitney U-test, Student's test, or a simple correlation test. Mean values are reported as the mean $\pm$ SD. Differences of $p < 0.05$ were considered statistically significant. The Kaplan-Meier method and Cox proportional hazard model were used for survival analyses.

Ethical Considerations

This retrospective study was approved by the Ethics Committee of Kagoshima University Hospital. We certify that this study involving human subjects is in accordance with the Helsinki Declaration of 1975 as revised in 2000 and with the Ethical Guidelines for Epidemiological Research (effective on July 1, 2002) by the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labor and Welfare, Japan. To protect patient privacy, all data were collected and analyzed after anonymization in an unlinkable fashion.

Results

Demography

Scrupulous collation found that 8 cases were reported twice from different institutions. Therefore, a total of 201 patients with PMs were included in this study (male/female 109:92). The patients' ages ranged from 26 to 85 years with a mean of 59.0 ± 11.4 years (error rate 1.4%). The age of 1 patient was not reported. The most common age group was the 60- to 64-year group, followed by the 55- to 59-year group (Fig. 1). The average age of the 108 male patients was 61.1 ± 10.7 years (error rate 1.7%), and that of the 92 female patients was 56.5 ± 11.7 years (error rate 2.7%).

Diagnosis of PM

It was noteworthy that the diagnosis of PM was histologically verified in only 69 patients (34.3%). These patients were classified as the "definite group." In the other 132 patients (65.7%), the PM was diagnosed by their physicians-in-charge based on neuroimaging findings, clinical presentation, clinical course, and an increase in blood tumor markers, and combinations of these factors. These

FIG. 1. Age distribution of patients with pituitary metastases (n = 200). Age was not listed for 1 patient. The majority (83.6%) of patients were between 45 and 74 years of age.

nonhistologically verified tumors were classified as the “nondefinite group.”

Primary Tumor Sites

In the 201 patients, the most frequent primary tumor was lung cancer (36.8%), followed by breast (22.9%), kidney (7.0%), and colorectal (6.5%) cancer (Fig. 2). Among 109 men, lung cancer was the most frequent primary tumor (45.9%), followed by kidney (11.0%), lymphatic (8.3%), liver (7.3%), and colorectal (4.6%) cancer (Fig. 3 left). Among 92 women, breast cancer was the most frequent (50.0%), followed by lung (26.1%) and colorectal (8.7%) cancer (Fig. 3 right).

Interval Between the Diagnosis of Primary Tumor and PM

The interval between detection of the PM and primary tumor was reported in 157 cases. Detection of the pituitary lesion preceded the diagnosis of primary tumor in 17 of 157 cases (10.8%). In the remaining 140 patients, the average interval between diagnosis of the initial cancer and detection of the PM was 2.8 ± 3.9 years (error rate 11.8%). The interval was within 1 year in 45.0% (n = 63), 1–3 years in 22.9% (n = 32), 3–5 years in 12.1% (n = 17), 5–10 years in 15.0% (n = 21), and longer than 10 years in 5.0% (n = 7) of the 140 patients. In 63 patients with a PM detected within 1 year after the diagnosis of primary tumor, the most frequent primary tumor was lung cancer (61.9%) followed by lymphoma (7.9%). On the contrary, among a total of 28 patients whose pituitary lesion was detected more than 5 years after the diagnosis of primary tumor, the most frequent primary tumor was breast cancer (53.6%) followed by colorectal (10.7%) and kidney (10.7%) cancer. Only 7.1% of this group of patients had lung cancer.

FIG. 2. Distribution of primary tumor site in total (n = 201).

Symptoms

Symptoms at the time of diagnosis of PMs greatly varied, with visual disturbance in 30.3%, diabetes insipidus in 27.4%, fatigue in 25.4%, headache in 20.4%, double vision in 17.4%, nausea/vomiting in 11.4%, consciousness disturbance in 8.0%, appetite loss in 6.5%, seizure in 1.5%, and cold intolerance in 1.0% of total cases (multiple answers were allowed for this question) (Fig. 4). It was noticeable that symptoms that are rarely seen in pituitary adenoma such as diabetes insipidus and double vision were not uncommon in this PM series.

Anterior Pituitary Functions

Hormone assays varied among institutions, and the assessment of pituitary function was left to the discretion of the participating physicians. Patients with hypoadrenocorticism, as judged by low serum cortisol levels or newly initiated hydrocortisone replacement, accounted for 42.3% (85/201) of all and those with hypothyroidism, as judged by low serum thyroxine levels or newly initiated levothyroxine replacement, accounted for 43.3% (87/201) of all. Among 54 patients whose insulin-like growth factor level was measured, 26 (48.1%) showed low levels, less than –2 standard deviations of the age- and sex-matched normal population. The gonadal function was not included in the questionnaire due to the difficulty of judging its function solely by the levels of sex steroids.

Neuroimaging Findings

All patients underwent MRI. Mass lesions in other intracranial sites were seen in 45.0% (81/180; denominator in this paragraph is the total number of responses to each particular question [Table 1]). Among 180 patients who

Origin	Numbers	%
Lung	74	36.8
Breast	46	22.9
Kidney	14	7.0
Colon/rectum	13	6.5
Lymph	10	5.0
Unknown	9	4.5
Liver	8	4.0
Stomach	4	2.0
Thyroid	4	2.0
Larynx/pharynx	3	1.5
Parotid gland	3	1.5
Thymus	2	1.0
Blood	2	1.0
Esophagus	2	1.0
Gallbladder/bile duct	1	0.5
Adrenal gland	1	0.5
Uterine tube	1	0.5
Bladder	1	0.5
Pancreas	1	0.5
Prostate	1	0.5
Retroperitoneum	1	0.5

FIG. 3. Distribution of primary tumor by sex.

underwent MRI with gadolinium contrast, 176 (97.8%) tumors were well enhanced, while 4 (2.2%) tumors were poorly enhanced. The incidence of MRI findings, according to the physicians or radiologists who evaluated the images, were as follows: mass lesion in the pituitary stalk, 63.7% (107/168); dumbbell shape or constriction of tumor at diaphragmatic hiatus (Fig. 5), 44.7% (80/179); loss of hyperintensity in neurohypophysis, 82.3% (107/130); contrast enhancement of dura mater around the pituitary fossa, 17.1% (29/170); hypothalamic mass lesion, 17.4% (30/172); hyperintensity in the optic tract with or without the internal capsule (Fig. 6), 11.5% (17/148); and intratumoral bleeding, 8.5% (15/176).

Size and Direction of Extension in PM

The size of the PMs, reported in 185 cases, ranged from 1 to 60 mm with mean of 20.9 ± 10.6 mm (error rate 3.7%). The mean length of upward extension of the tumor (Fig. 7), that is, the distance of uppermost part of tumor from the line connecting tuberculum sellae and tip of dorsum sellae (TD line), was 12.8 ± 8.6 mm (error rate 4.9%). The mean length of upward extension of PMs was longer than that of 50 nonfunctioning pituitary adenomas (10.3 ± 6.5 mm, error rate 8.9%), which we previously reported,¹ but statistically insignificant ($p = 0.12$, Mann-Whitney U-test). The length of downward extension (Fig. 8), the distance of the lowermost part of the tumor from the standardized sellar floor, which is 7.2 mm deeper from the TD line,^{1,30} was 3.0

FIG. 4. Frequency of clinical symptoms. Values on the y axis represent the percentage of patients.

± 3.9 mm (error rate 9.6%), which was significantly shorter than that of 50 nonfunctioning adenomas (8.9 ± 4.5 mm, error rate 7.2%)¹ ($p < 0.01$, Mann-Whitney U-test) (Fig. 8).

Control of Primary Tumor

The status of primary tumor control was available in 162 patients. At the time of diagnosis of PM, the primary lesion was thought to be under control in 37.0% (60/162) of the reported patients.

Treatment of PM

As for treatment, surgery was performed in 26.9% (54/201) of the patients and radiotherapy targeting the PM was performed in 74.6% (150/201) of total patients. Of these 150 patients, 80.0% (120/150) underwent stereotactic radiotherapy including Gamma Knife in 108 patients, CyberKnife in 11 patients, and stereotactic linear accelerator in 1 patient. For Gamma Knife surgery, a median peripheral dose of 18.0 Gy was given in most cases in a single session, with an average dose of 16.7 ± 4.8 Gy. Two or three sessions of Gamma Knife surgery were performed in 3 patients. For CyberKnife treatment, a median peripheral x-ray dose of 30 Gy was given in 3–8 fractions, with an average dose of 28.0 ± 5.9 Gy. External beam x-ray radiation was given in 30 patients with a median dose of 40 Gy in 18 fractions. In 6 patients, the second stereo-

TABLE 1. Findings on MRI

Finding	No. of Answers to the Question	No. of Patients w/ Finding (%)
Other intracranial lesions	180	81 (45.0)
Hypothalamic mass	172	30 (17.4)
Mass in pituitary stalk	168	107 (63.7)
Loss of hyperintensity of neurohypophysis	130	107 (82.3)
Hemorrhage in the tumor	176	15 (8.5)
Constriction of tumor at diaphragmatic hiatus	179	80 (44.7)
Hyperintensity around optic tract	148	17 (11.5)
Contrast enhancement of surrounding dura mater	170	29 (17.1)

FIG. 5. Coronal (left) and sagittal (right) MR images of a histologically verified pituitary metastasis from lung cancer showing a constriction at the diaphragmatic hiatus (arrows) of tumor leading to the dumbbell shape.

tactic radiation session was performed using the Gamma Knife or CyberKnife for recurrence of the lesion.

Chemotherapy was instituted in 9.0% (18/201) of the patients after the diagnosis of PM. Treatment targeted to the PM was not given in 15.4% (31/201) of patients.

As for treatment complications, surgical complications were documented in 5 patients (9.3%) among 54 surgeries: 3 in transsphenoidal surgery and 2 in transcranial surgery. Surgical morbidity included hypopituitarism, diabetes insipidus, visual disturbance, and consciousness disturbance. Radiation-induced morbidity was reported in 10 patients (6.7%) among 150 patients who underwent initial radiotherapy. These included emesis, hypopituitarism, diabetes insipidus, and visual disturbance.

Consecutive changes in tumor size of PMs for 1 year after radiation therapy were reported in 73 patients. Tumor size decreased in 78.1% (57/73), increased in 9.6% (7/73), and was unchanged in 12.3% (9/73) during the first 6 months. In 7 patients, the tumor size increased after the initial decrease during 1 year after the radiation therapy.

Mortality and Cause of Death

During the follow-up time ranging from 0.3 to 125.3 months with a mean of 14.0 ± 19.6 months (error rate 10.9%), among 165 patients whose prognosis was reported 91 (55.2%) died. The cause of death was progression of the primary tumor in 51.6% (47/91), extracranial metastatic lesion in 17.6% (16/91), intracranial extrapituitary metastatic lesions in 5.5% (5/91), aggravation of the pituitary lesion in 13.2% (12/91), and not specifically reported in 1.1% (1/91).

Survival Analysis

For the survival analysis, detailed information of 165 patients was collected. The overall median survival time was 12.9 months. Survival rates at 1, 2, and 3 years were 50.9%, 32.4%, and 28.2%, respectively (Fig. 9).

The median survival time largely varied depending on primary tumor: 8.9 months in 58 patients with lung cancer, 25.6 months in 41 patients with breast cancer, and 33.4 months in 13 patients with renal cancer (Fig. 10A). The Kaplan-Meier survival curve showed significantly better survival in patients with breast cancer and renal cell cancer than in those with lung cancer ($p = 0.0012$, log-rank test).

FIG. 6. Fluid attenuated inversion recovery MR image of a histologically verified pituitary metastasis from lung cancer showing hyperintensity alongside the optic tract (arrows).

The status of control of primary tumor affected the survival. The median survival time of patients with good control of primary tumor ($n = 52$) was 46.2 months and that of patients with poor control ($n = 86$) was only 10.2 months; the difference is statistically significant ($p = 0.0014$, log-rank test) (Fig. 10B).

The survival rate of patients older than 70 years was significantly poorer than that of younger population, with median survival times of 16.8 months in 40 patients 25–49 years old, 18.3 months in 45 patients 50–59 years old, 9.1 months in 55 patients 60–69 years old, and 6.9 months in 25 patients 70–85 years old ($p = 0.0059$, log-rank test) (Fig. 10C). The survival rate for women tended to be better than that for men ($p = 0.0809$), with median survival times of 16.8 and 9.1 months in 76 women and 89 men, respectively.

In 123 patients treated with radiation therapy, the median survival time was significantly better (16.4 months) than in 42 patients not treated with radiation (6.4 months; $p = 0.0001$) (Fig. 10D). The median survival time in 24 patients who underwent conventional multifractionated external beam radiotherapy was 16.1 months and that in 97 patients who underwent stereotactic radiation was 18.7 months; the survival curves were almost overlapped ($p = 0.743$, log-rank test).

Clinical Features of Definite Group and Nondefinite Group

To elucidate the clinical features of 132 patients whose tumors were not histopathologically diagnosed (the nondefinite group), the following comparisons were conducted (Table 2). In the nondefinite group, the lung was the site of the primary tumor in 43.9% (58/132) of nondefinite cases and in 23.2% (16/69) of definite cases. Diagnosis of the PM preceded that of the primary lesions in 6.1%

FIG. 7. Upward extension of pituitary metastasis in comparison with clinically nonfunctioning adenoma. D = dorsum sellae; T = tuberculum sellae.

(8/132) of cases in the nondefinite group and 13.0% (9/69) of cases in the definite group. The interval until the detection of the PM was less than 1 year in 37.4% (49/132) of patients in the nondefinite group and in 20.3% (14/69) of patients in the definite group. The mean interval was significantly shorter in the nondefinite group than in the definite group (2.0 ± 3.2 years [error rate 17.7%] vs 3.5 ± 4.6 years [error rate 16.0%]; $p = 0.0183$, Student *t*-test). The presence of other intracranial lesions was more frequently observed in the nondefinite group (47.0% [62/132]) than in the definite group (27.5% [19/69]) at the time of diagnosis of PM. The survival time was marginally shorter in the nondefinite group than in the definite group ($p = 0.895$, log-rank test), with a median survival time of 11.4 months versus 13.8 months.

Contributing Factors on Survival Rate

For Cox proportional hazard analysis, 133 sets of data were available with information regarding age, sex, interval between the diagnosis of primary tumor and PM, control status of the primary lesion, maximum diameter of the

PM, presence of other intracranial lesions, chemotherapy, and radiotherapy (Table 3). In summary, the following were independent factors for better prognosis (hazard ratio < 1 , $p < 0.05$): young age, late metastasis to the pituitary gland, smaller size of the PM, and radiation therapy. Control state of the primary lesion tended to affect the survival ($p = 0.0507$).

Discussion

We conducted a nationwide questionnaire survey covering almost all endocrinology and neurosurgery institutions as well as stereotactic radiation centers in Japan to characterize the current clinical features of PMs. Through this study, some contemporary aspects of this disease were elicited.

Clinical Features of PMs

The most frequent primary tumor of symptomatic PM has been reported to be breast cancer.^{16,19,20,28} However, in this survey, overall the most frequent primary tumor was

FIG. 8. Downward extension of pituitary metastasis in comparison with clinically nonfunctioning adenoma.

FIG. 9. Survival curve (Kaplan-Meier) of total reported patients ($n = 165$). MST = median survival time.

lung cancer (36.8%), followed by breast cancer (22.9%), although breast cancer was still the most frequent (50.0%) in women. It is also noteworthy that the incidence of prostate cancer, which was generally reported as the third primary tumor in previous series,^{7,16} was as low as 0.5% in our series. There were no cases of melanoma in this series.

These findings may be a reflection of the relatively low prevalence of these cancers in the Japanese population or in Mongolia.^{2,12,29}

A review of 190 symptomatic PMs by Komninos et al. showed that in 83 (43.7%) cases the primary tumor was latent when the PM was discovered.¹⁶ This figure might be influenced by the multiple reports describing rare presentations.¹⁶ In our series, primary tumors were generally diagnosed before the detection of PMs; the pituitary lesions were detected before the original tumor in only 10.8% of cases. The mean intervals for detection of PM widely varied depending on the primary tumor: 0.68 years for lung cancer, 2.84 years for kidney cancer, and 4.76 years for breast cancer. Therefore, the usual 5-year limit could not be set to preclude the possibility for less aggressive tumor such as breast or colorectal cancer to metastasize into the pituitary gland.

Imaging Diagnosis

Pituitary adenoma is benign and the most common sellar tumor, which accounts for 76.4% of pituitary gland-chiasmatic region tumors.⁵ Therefore, the preoperative differentiation of PM from pituitary adenoma based on imaging studies has critical importance.

FIG. 10. Survival curve analysis (Kaplan-Meier) according to possible prognostic factors. **A:** Primary tumors ($n = 112$). **B:** Control of primary tumor ($n = 138$). **C:** Patients' age in years ($n = 165$). **D:** Radiotherapy ($n = 165$).

TABLE 2. Comparison of clinical features between the definite group and nondefinite group

Variable	Definite Group (n = 69)	Nondefinite Group (n = 132)
Primary tumor		
Lung	23.2%	43.9%
Breast	23.2%	22.7%
Kidney	7.2%	6.8%
Colon/rectum	10.1%	4.5%
Lymphatic	5.8%	4.5%
Unknown	2.9%	5.3%
Interval btwn diagnosis of primary tumor & PM in yrs		
0–1	20.3%	37.4%
1–3	17.4%	15.3%
3–5	7.2%	9.2%
5–10	15.9%	7.6%
>10	5.8%	2.3%
PM preceded primary lesion	12.9%	6.1%
Unknown	20.3%	22.7%
Mean	3.5 ± 4.6	2.0 ± 3.2*
Other intracranial metastatic lesion	27.5%	47.0%
Median survival time in mos	13.8	11.4†

* p = 0.0183, Student t-test.

† p = 0.895, Log-rank test.

Some imaging features suggestive of PM have been reported. Constriction at the diaphragma sellae, documented in 44.7% (80/179) of cases in our series, was reported to be 10% by Komninos et al.¹⁶ The difference in incidence seems to be deeply affected by the authors' awareness of this finding. It was seen in all of 4 PMs reported by Schubiger and Haller.²⁶ The constriction or dumbbell shape may reflect infiltrative growth of the malignant tumor, which passes through the diaphragmatic hiatus without enlarging it and grows under and above it. Edema along the optic chiasm and tract was first described in a craniopharyngioma case and soon reported to be seen in other sellar lesions including PM but rarely seen in pituitary adenoma.²⁵ In this study, it was seen in 11.5% of cases.

Bony changes, such as erosion of surrounding bony structures and sellar enlargement, are well-known findings.^{16,20} Kistler and Pribram reported that enlargement of the sella precludes the possibility of PM.¹⁵ The study showed that the length of inferior extension was significantly smaller in PMs, while the length of upward growth was larger than nonfunctioning pituitary adenomas. A PM may manifest clinical symptoms before enlargement of the sella turcica by rapid growth in an upward direction.

Treatment

Microscopic or endoscopic transsphenoidal surgery may quickly improve ophthalmological symptoms.^{20,23} However, sufficient decompression may be occasionally hindered by the fibrous component of the tumor or excessive bleeding.^{7,11,16,21,24,27} Considering that progression of

TABLE 3. Hazard ratios of presumptive prognostic factors influencing survival in patients with PM*

Variable	df	Item	p Value	HR
Age (yrs)	1		0.0012	1.034
Sex (male, female)	1	Female	0.1262	0.663
Interval until pituitary metastasis (yrs)	1		0.0010	0.708
Control of primary lesion (good, poor, unknown)	2		0.0507	
	1	Good	0.5615	0.741
	1	Poor	0.3159	1.611
Maximum diameter of pituitary lesion (mm)	1		<0.0001	1.205
Other intracranial metastasis (present, no, unknown)	2		0.6464	
	1	Present	0.3977	0.677
	1	No	0.3622	0.656
Chemotherapy (yes, no)	1	Yes	0.7633	0.894
Radiotherapy (yes, no)	1	Yes	0.0370	0.522

* Factors and values in boldface are statistically significant (p < 0.05).

the pituitary lesion itself was the cause of death in only 13% of patients, the surgical eradication of the pituitary lesion may not significantly benefit the overall survival.^{16,20,23}

Currently, 58 Gamma Knife units are in service in Japan (information from personal contact with distributors). In this series, 59.7% (120/201) of the patients received stereotactic irradiation. Iwai and colleagues reported that 6 of 7 patients achieved regional control and improvement of symptoms after stereotactic radiotherapy with a marginal dosage of 10–14 Gy (mean 11.9 Gy) using the Gamma Knife.¹³ Kano et al. reported their experience of treating 18 patients who harbored PMs using the Gamma Knife.¹⁴ Although the overall survival was limited, the lesions were well controlled and new symptoms due to tumor progression were demonstrated in only 3 patients.¹⁴

Considering limited survival time of the patients, poor general condition, and the noninferiority to conventional multiple fractionated radiation in terms of median survival time (see *Survival Analysis*), stereotactic radiation may become the first choice of radiation treatment for PMs in cases without multiple intracranial metastases.

Prognosis

The prognosis for patients with PMs is poor, not because of the location per se but because of the advancing stage of the primary cancer.^{16,20} Furthermore, at the time of diagnosis, more than half of the patients have systemic metastasis.^{9,11,14,18,20} Median survival reported in previous series ranged from 6 to 11 months;^{11,13,16,18,20} survival rarely surpassed 3 years.²² However, in the series of Morita et al., 3 of 36 patients survived at 5 years following diagnosis.²⁰ A very recent report also showed a prolonged median survival time of 11.8 months (ranging from 3 to 43 months) in a series of 15 PMs.³¹ The median survival time was 12.9 months in our series. Given that only 13.2% of patients died of progression of the pituitary lesion, the improved survival may have been due to development of systemic treatment and management for advanced cancer.

The elongation of the survival will necessitate the change of management strategy for patients with PMs,

from terminal care to long-term maintenance of quality of life. In this context, appropriate treatment of pituitary dysfunction, including gonadotropin as well as cortisol and thyroxine levels, which is rarely recovered by treatment aimed at the pituitary lesion, is essential.²⁰

Limitations of This Study and Future Study

First, it was surprising that more than 60% of the patients were diagnosed with PMs based on neuroimaging findings, clinical presentation, clinical course, and an increase in blood tumor markers, or combinations thereof, and not based on histological evidence. In this group, referred to as the nondefinite group, we cannot exclude a possibility that non-PM cases such as pituitary incidentaloma were included in the cohort. However, this group had more biologically aggressive primary tumors such as lung cancer, more advanced cancer stage, and shorter interval until the detection of PM (see *Results*). These conditions might have led to poorer general condition precluding biopsy surgery in the nondefinite group. Recent reports on PM also include a large proportion of nondefinite group of diagnosis.^{13,14} We now know that many clinicians diagnosed some PMs without histological evidence and managed these cases based on their tentative diagnoses. We need more detailed clinical and imaging data leading to diagnosis of PMs without pathology to get a holistic understanding of nondefinite PMs. Second, we could not include the analyses of patients' performance status and quality of life, which is mandatory to select proper treatment for this serious illness and should be a task in future studies. Third, due to the retrospective nature of this study, there were frequent missing values in clinical and radiological data, which might have distorted the true figures of the PMs. Fourth, we cannot elicit the rate of pituitary metastasis for each kind of malignant neoplasm due to the low response rate to the questionnaire (50% in hospital base), which may cause considerable selection bias. Furthermore, there is a high probability that many patients with PMs were cared for in small clinics and palliative care centers, to which the questionnaire was not sent, without consulting specialists. Future population-based surveys should be, thus, prospective and inventory.

Conclusions

An analysis of 201 cases reported as pituitary metastasis in Japan showed that the most frequent primary tumor was lung cancer followed by breast cancer. Almost 60% of the patients underwent stereotactic radiation for controlling the pituitary lesion. Median survival time was substantially longer, 12.9 months, compared with previous reports. Half of the deaths were caused by progression of the primary lesion, followed by extracranial and intracranial metastases. Only 13.2% of patients died due to an aggravation of pituitary lesion. Considering that more than half of the patients survive longer than a year, PM patients should not be always subjected to terminal-stage care. Appropriate appraisal of pituitary dysfunction and its pertinent replacement are mandatory. The treatment modality should be elucidated by future studies in the light of survival and better quality of life.

Acknowledgments

We highly appreciate the physicians who kindly sent case records to us: members of The Japan Endocrine Society, members of The Japanese Society for Hypothalamic and Pituitary Tumors, and doctors belonging to stereotactic radiation centers (see *Appendix*).

We declare that each of us acknowledges that he or she participated sufficiently in the work to take public responsibility for the content of this paper.

Appendix

Physicians who reported cases with pituitary metastasis: Kosaku Amano, Daisuke Aono, Noriaki Fukuhara, Noriaki Hanyu, Hironobu Harada, Yuji Hataya, Michio Hayashi, Motohiro Hayashi, Yasuhiko Hayashi, Hisao Hirai, Kentaro Horiguchi, Kaoru Ichihara, Hidetoshi Ikeda, Chie Inomoto, Akihiro Inoue, Yasuhiro Inoue, Kenichi Ishibashi, Eiji Itagaki, Miiko Ito, Toshihiko Iuchi, Yoshiyasu Iwai, Naoko Iwata, Hidefumi Jokura, Teruyoshi Kageji, Wataru Kameda, Tadashige Kano, Junko Kato, Toshiro Katsuta, Jun Kawagishi, Takakazu Kawamata, Hirotsugu Kawamoto, Ryogo Kikuchi, Toshikazu Kimura, Yasuyuki Kinoshita, Atsushi Kiyota, Ryuhei Kitai, Yasato Komatsu, Takeshi Kondo, Atsushi Kuge, Kazuhiko Kurozumi, Hiroyuki Masaoka, Yuka Matoba, Akira Matsuno, Takayuki Matsuo, Misaki Miyata, Katsuharu Mori, Yoshimasa Mori, Ryo Morikawa, Tetsuya Nagatani, Yasushi Nagatomo, Mizuho Nakagawa, Takuo Nanbu, Shigeki Nishino, Ryutaro Nomura, Koichiro Ogawa, Hisayo Okamoto, Kazuya Okamoto, Takahiro Okusu, Hiroaki Onishi, Naokatsu Saeki, Yoshinori Saika, Katsuya Saito, Keiichi Sakai, Tetsuro Sameshima, Kengo Sato, Masahiro Shin, Shuji Shinkawa, Junji Shinoda, Hitoshi Sugihara, Nami Suzuki, Satoshi Suzuki, Shigeyuki Tahara, Masashi Takagi, Shingo Takano, Yoshiyuki Takeda, Susumu Takekoshi, Nobuo Takenaka, Masahi Tamaki, Tetsuro Tamura, Koshi Tatewaki, Kinya Terada, Yuzo Terakawa, Masahiro Toda, Masahiko Tosaka, Nagaoki Toyoda, Kumiko Tsuboi, Masashi Uchida, Hiroki Udono, Tetsuya Ueba, Kenta Ujifuku, Kiyoaki Uryu, Takeshi Usui, Masayo Yamada, Hideki Yamaguchi, Junkou Yamamoto, Tetsuo Yamashita, Shigetoshi Yano, Soichiro Yasuda, Kazutaka Yatsushiro, Tadato Yonekawa, Yuichiro Yoneoka, Mitsuhiro Yoneya, Masanori Yoshida, Miyako Yoshizawa.

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