The outcomes of conservatively observed asymptomatic nonfunctioning pituitary adenomas with optic nerve compression

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OBJECTIVE The authors investigated the natural history of asymptomatic nonfunctioning pituitary adenomas (NFPAs) with optic nerve compression.

METHODS This study retrospectively analyzed the natural history of asymptomatic NFPAs with documented optic nerve compression on MRI diagnosed between 2000 and 2016 from 2 institutions. The patients were followed up with regular endocrinological, ophthalmological, and radiological evaluations, and the endpoint was new endocrinopathy or neurological deficits.

RESULTS The study comprised 81 patients. The median age at diagnosis was 58.0 years and the follow-up duration was 60.0 months. As the denominator of overall pituitary patients, 2604 patients were treated with surgery after diagnosis at the 2 institutions during the same period. The mean initial and last measured values for tumor diameter were 23.7 ± 8.9 mm and 26.2 ± 11.4 mm, respectively (mean $\pm$ SD). Tumor growth was observed in 51 (63.0%) patients; however, visual deterioration was observed in 14 (17.3%) patients. Ten (12.3%) patients experienced endocrine deterioration. Fourteen (17.3%) patients underwent surgery for either visual deterioration (in 12 patients) or endocrine dysfunction (in 2 patients). After surgery, all patients experienced improvements in visual or hormonal function. The actuarial rates of treatment-free survival at 2, 3, and 5 years were 96.1%, 93.2%, and 85.6%, respectively. In the multivariate analysis, initial cavernous sinus invasion (HR 4.985, 95% CI 1.597–15.56; $p = 0.006$) was the only independent risk factor for eventual treatment.

CONCLUSIONS The neuroendocrinological deteriorations were not frequent and could be recovered by surgery with early detection on regular follow-up in asymptomatic NFPAs with documented optic nerve compression on MRI. Therefore, conservative management could be an acceptable strategy for these tumors. Careful follow-up is required for tumors with cavernous sinus invasion.

<https://thejns.org/doi/abs/10.3171/2020.4.JNS192778>

KEYWORDS pituitary adenoma; nonfunctioning; optic nerve; observation; natural history; pituitary surgery

PITUITARY adenomas are benign neoplasms of the pituitary gland and are relatively common in clinical practice.¹ In the general population, the estimated prevalence of pituitary adenomas is approximately 10%, but a prevalence of 27% has been reported.^{2–4} Many of these lesions are incidentally detected with advances in imaging techniques, and affected patients typically present with syndrome of hormone hypersecretion and/or signs re-

lated to mass effect, depending on tumor size.⁵ Mass effects may lead to serious clinical symptoms such as visual impairments, chronic headache, and pituitary insufficiency. In particular, visual involvement is crucial, and at the time of initial diagnosis visual field defects (VFDs) are detected in 60%–80% of patients with pituitary macroadenomas.⁶

Symptomatic mass effects are absolute surgical indications for nonfunctioning pituitary adenomas (NFPAs).

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; GH = growth hormone; GTR = gross-total removal; HR = hazard ratio; NFPA = nonfunctioning pituitary adenoma; RGC = retinal ganglion cell; TSH = thyroid-stimulating hormone; VFD = visual field defect.

SUBMITTED October 13, 2019. **ACCEPTED** April 6, 2020.

INCLUDE WHEN CITING Published online June 5, 2020; DOI: 10.3171/2020.4.JNS192778.

After tumor resection, improved vision was reported in 80%–90% of cases (including both partial and total recovery); recovery of normal anterior pituitary function is provided in approximately 30% of cases.⁷ However, it is crucial to point out that transsphenoidal surgery is associated with major complications, such as CSF leakage, meningitis, new hormone deficiency, and persistent diabetes insipidus in < 5% of cases and mortality in < 1% of cases.⁴ Therefore, in cases of asymptomatic NFPAs the question of management arises, whether by surgery or surveillance.

Several previous studies have reported the natural history of NFPAs, yet most of those reports have been limited by small sample size and heterogeneity. Only a few studies have reported the natural course of clinically nonfunctioning macroadenomas and seldom have assessed the tumors with optic nerve compression, mainly because most patients with macroadenomas are surgically treated.² Previous studies divided pituitary adenomas into only micro- or macroadenomas and involved many tiny pituitary adenomas in study cohorts. Under these circumstances, asymptomatic patients who have NFPAs with optic nerve compression are not uncommonly met in clinical practice. These individuals do not always have visual symptoms, and there is the question of whether an operation is mandatory. It has long been a question and would be helpful to know the clinical outcome for those patients followed with a “wait-and-see” policy. This study evaluated the natural history of asymptomatic NFPAs with optic nerve compression on imaging studies.

Methods

Patient Population

This retrospective cohort study was approved by the institutional review board. The authors identified patients diagnosed with NFPAs with evidence of optic chiasm compression on imaging studies at their institutions between 2000 and 2016. The criteria for inclusion were as follows: 1) imaging features of the pituitary adenoma with documented optic nerve compression on MRI (Fig. 1); 2) no clinical or biochemical evidence of hormone excess; 3) at least 1 sequential MRI obtained during the follow-up periods with at least a 12-month interval; 4) no previous management history for pituitary lesions; and 5) regular endocrinological and ophthalmological follow-up. Given that this study was intended to evaluate the natural history of NFPAs with optic nerve compression, patients should have displacement of the visual pathways in contact with the tumor on initial MRI. The patients had no symptoms related to pituitary adenomas at the time of diagnosis, not only for the visual field, but for endocrine issues such as loss of libido or amenorrhea, etc. We excluded patients with imaging features suggestive of Rathke cleft cyst or craniopharyngioma, or with a history of previous surgery or radiation.

Follow-Up Protocol

The follow-up duration was defined as the period between the time of diagnosis and the last MRI session. All patients underwent follow-up MRI of the sellar region annually during the first 2 years after the diagnosis of

NFPAs. Patients whose tumor size changed during the first 2 years underwent MRI every year thereafter; MRI was performed every 2 years for the patients in whom there was no change in tumor size during the first 2 years. If the patient had new symptoms of visual deterioration or pituitary apoplexy during the follow-up, they underwent MRI and ophthalmological assessments immediately. If a visual disturbance was suspected to be due to a tumor, then resection was performed. The primary outcome of the present study was eventual treatment due to visual or endocrine deterioration caused by mass effect, leading to surgery after observation.

Comparing the first and the last MRI studies, the following parameters were measured: 1) cavernous sinus invasion (T1-weighted coronal MRI, Knosp grade 3 or higher); 2) micro- or macroadenoma (T2-weighted coronal, sagittal, and axial MRI); 3) cystic or solid lesion (T2-weighted coronal MRI, cystic portion > 30%); and 4) tumor volume (T2-weighted coronal MRI). Tumor volume was estimated from the volumetric measurement of the coronal MRI with 1-mm slice thickness: the tumor area was determined by tracing its contour on each MRI slice, and then the volume was calculated by multiplying the sum of the areas by the slice thickness. The accuracy of measurements by this method has been validated in previous studies.^{3,4} Regarding tumor size, the final volume with an increase or a decrease of 20% relative to the initial volume was regarded as growth or shrinkage, respectively.

At diagnosis, basal levels of growth hormone (GH), insulin-like growth factor-I, adrenocorticotrophic hormone (ACTH), serum cortisol, free T4, thyroid-stimulating hormone (TSH), prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol, and total testosterone were measured by radioimmunoassay and immunoradiometric assay between 8 and 10 AM. A rapid ACTH stimulation test was performed for patients with suspected adrenal insufficiency. During the follow-up, endocrine function was evaluated in all patients with at least a 6-month interval, as previously described.⁴ Endocrine deterioration was a loss of ≥ 1 of the hormonal axis during the follow-up. Improved endocrine dysfunction was a gain of ≥ 1 of the hormonal axis during the follow-up. Loss or gain of hormonal axis was defined biochemically, not by whether hormone replacement was initiated. The finding of hypopituitarism can only be considered a relative indication for surgery because the reversal of hypopituitarism by surgery is not 100% assured and because the hypopituitarism itself is treatable with hormone replacement.⁸

At each clinical visit, the patients were carefully interviewed to assess whether any subjective symptoms suggesting visual impairment had developed. Additionally, ophthalmological assessments consisting of visual acuity and field testing were conducted at the time of the initial diagnosis and then at 6-month intervals. For patients whose tumor size was stable during the first 2 years, ophthalmological evaluation was performed every year thereafter. Patients whose tumor size was suspected to have increased maintained at least 6-month intervals for ophthalmological and hormonal assessments. The visual field was evaluated using the Goldmann visual field test or the

FIG. 1. Example images of a patient in this study. This 78-year-old woman underwent brain MRI for impaired cognition. Coronal (A) and sagittal (B) images showed pituitary adenoma with optic chiasm compression. However, the patient had an unaffected visual field on ophthalmological examination (C). Figure is available in color online only.

Humphrey visual field analyzer. Visual deterioration was defined as any new-onset VFD.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 25; IBM Corp.), and differences with a p

value < 0.05 were considered statistically significant. The categorical variables were presented as the number of patients (%) and the continuous variables as the mean ± SD. Comparisons between the 2 groups were performed using the Student t-test for numerical variables and the chi-square test for categorical variables. The Kaplan-Meier

TABLE 1. Baseline characteristics of the study population and comparison between patients eventually discharged after observation and those who had maintained stable status

Characteristics	Total Patients	Treatment Group	Stable Group	p Value
No. of patients	81	16 (19.8%)	65 (80.2%)	NA
Age, yrs	58.1 ± 12.9	58.1 ± 9.43	58.1 ± 13.7	0.997
Male	48 (59.3%)	10 (62.5%)	38 (58.5%)	0.768
Follow-up duration, mos	65.7 ± 38.0	50.3 ± 21.2	65.9 ± 40.5	0.139
CS invasion	36 (44.4%)	12 (75.0%)	24 (36.9%)	0.006
Cystic tumor	7 (8.6%)	1 (6.3%)	6 (9.2%)	1.000
Tumor vol, cm ³				
At Dx	4.38 ± 3.30	4.63 ± 3.46	4.32 ± 3.28	0.739
On last follow-up	6.91 ± 9.60	7.11 ± 4.55	6.86 ± 10.5	0.926
Tumor growth	51 (63.0%)	14 (87.5%)	37 (56.9%)	0.023
Visual det	14 (17.3%)	14 (87.5%)	0 (0.0%)	<0.001
Endocrine det	10 (12.3%)	2 (12.5%)	8 (12.3%)	1.000

CS = cavernous sinus; det = deterioration; Dx = diagnosis; NA = not applicable.

Data are presented as the mean ± SD or the number of patients (%). Boldface type indicates statistical significance.

survival curve with the log-rank test was presented. A multivariate analysis was performed using the Cox regression model to determine the hazard ratio (HR) of risk factors for eventual treatment.

Results

Patient Characteristics

We identified 81 consecutive patients; their baseline characteristics are shown in Table 1. The mean age was 58.1 ± 12.9 years (median 58.0, range 15–81 years), and men accounted for 59.3% (n = 48) of the patients. The mean follow-up duration was 65.7 ± 38.0 months. Most of the tumors were incidental findings (60.5%, n = 49); 27.2% (n = 22) of the patients had headaches that were not associated with tumors and were well controlled with medication; and 6.2% (n = 5) of the patients had visual symptoms that were not relevant to mass effects but were due to ophthalmological problems. The prevalence of tumors with cavernous sinus invasion and that of tumors with cystic portions were 44.4% (n = 36) and 8.6% (n = 7), respectively.

Endocrinological and Ophthalmological Results

Ten (12.3%) patients showed hormone deterioration at any axis: 6 (7.4%) patients with ACTH axis, 5 (6.2%) patients with TSH axis, and 1 (1.2%) patient with GH axis. In our cohorts, 1 (1.2%) patient experienced silent pituitary apoplexy presenting with hyponatremia due to hypocortisolism during follow-up periods. The patient had no visual symptoms and had hormone replacement without surgery, which resulted in a good clinical outcome. Among the 10 patients with hormone deterioration, 8 had no symptoms under medical treatment; however, the remaining 2 patients required resection for endocrine dysfunction, possibly due to mass effect.

Fourteen (17.3%) patients eventually experienced visual deterioration with a mean interval of 50.5 ± 22.1

months from the time of diagnosis. The remaining 67 (82.7%) patients still had preserved vision during the mean follow-up period of 65.4 ± 40.1 months. Figure 2 presents the Kaplan-Meier survival curve for the vision preservation rate in patients. The actuarial rates of vision preservation at 2, 3, and 5 years were 96.1%, 94.7%, and 87.0%, respectively. There was a significant difference in visual preservation rate between patients with and those without tumor growth (Supplementary Fig. 1). However, in multivariate analysis, these rates showed no statistical significance.

Tumor Control

The mean tumor volume at the time of diagnosis was 4.38 ± 3.30 cm³ (range 0.13–15.3 cm³) and that at the last follow-up was 6.91 ± 9.60 cm³ (range 0.00–74.0 cm³). The mean initial and last measured values for tumor diameter were 23.7 ± 8.9 mm and 26.2 ± 11.4 mm, respectively. Tumor growth was observed in 51 (63.0%) patients and spontaneous tumor shrinkage was observed in 12 (14.8%) patients during the follow-up periods.

During the follow-up periods, 14 (17.3%) patients underwent tumor resection. The reason for having surgery was either visual deterioration for 12 (85.7%) patients, or endocrine deterioration for the remaining 2 (14.3%) patients (Table 2). The actuarial rates of treatment-free survival at 2, 3, and 5 years were 96.1%, 93.2%, and 85.6%, respectively. Among 14 patients with visual deterioration, 2 refused to undergo tumor resection. For the 14 patients who underwent surgery, 12 (85.7%) achieved gross-total removal (GTR) of tumor. Two (14.3%) patients were receiving hormone replacement for hypopituitarism, which was started before surgery, and 1 (7.1%) patient had experienced transient diabetes insipidus. There was no CSF leakage or meningitis. Eleven of 12 (91.7%) patients who underwent surgery showed improvement in the visual field test, regaining their completely normal preoperative status after surgery. The other patient recovered to nearly normal

FIG. 2. Kaplan-Meier curve of the vision preservation rate. Figure is available in color online only.

status in the visual field test after surgery. The other 2 patients, who underwent surgery for endocrine deterioration, showed hormone function recovery after tumor resection. No patients had a permanent neurological deficit during observation periods.

In the univariate analysis, initial cavernous sinus invasion ($p = 0.006$) and tumor growth ($p = 0.023$) were associated with clinical worsening leading us to quit observation among patients in whom a “wait-and-see” policy was in place. In the multivariate analysis, initial cavernous sinus invasion (HR 4.985, 95% CI 1.597–15.56; $p = 0.006$) was an independent and significant risk factor (Fig. 3).

Discussion

We have presented the natural history of patients with asymptomatic NFPA with optic nerve compression who were followed with a “wait-and-see” policy. This study observed that the overall incidence of vision deterioration was 17.3% ($n = 14$) during the mean follow-up duration of 65.7 months. In addition, tumors with cavernous sinus invasion were an independent risk factor for discharge after observation.

The presumed NFPA without symptoms seemed to have followed a benign course, and several previous studies have reported a conservative approach with careful follow-ups.^{2,6–9} The decision to carefully monitor NFPA will mainly depend on the mass effect of tumor growth over time. On average, 89% of microadenomas and 75% of macroadenomas remain stable over 2–8 years of follow-up.¹⁰ Even more important is how fast any symptom will happen when the tumors grow. In this study, although 51 (63.0%) patients showed tumor growth, only 14 (17.3%)

experienced visual deterioration. The Kaplan-Meier estimate curve for visual deterioration in Fig. 2 shows that visual dysfunction does not worsen more abruptly than expected even for the patients of NFPA with optic nerve compression at the time of diagnosis. We can easily assume that those tumors are not always an absolute indication for surgery when the patients have no symptoms. However, the decision was very carefully made. At the time of first growth a thorough discussion was made with the patients and guardians. Because the patients had no symptoms even as the tumor grew, they decided to continue being observed and to undergo short-term follow-ups. Patients who were elderly tended to be managed conservatively.

How fast the vision will worsen when the tumors compress the optic apparatus remains unclear. Compressive lesions at the optic chiasm can produce visual dysfunction as a result of damage to retinal ganglion cells (RGCs) and their axons. Given that damage to RGCs does not occur via a direct process, but rather is the consequence of retrograde degeneration, visual field changes may precede ganglion cell loss in compression syndrome. The time difference between axonal injury and later loss of RGCs has not yet been proven, but some reported ganglion cell atrophy was prolonged for various times from 3 to 6 months.¹¹ The degree of visual dysfunction and recovery after surgical decompression is dependent on the amount of injury and recovery of RGCs. Therefore, visual dysfunction does not always mean a surgical emergency, but instead a need for thorough evaluation to determine the optimal time to decide treatment. When surgery was performed in a timely manner, clinical outcomes were acceptable. A previous study showed that in the case of the development of a VFD, surgical outcome is still favorable with respect to this condition.⁶ Additionally, in our series, all the patients who underwent surgery for new symptoms showed improvement after treatment. Careful monitoring and selection of patients for surgical intervention with regular MRI and vision test follow-up is reasonable.

In NFPA with optic nerve compression in which observation was the initial choice, it is important to evaluate them exactly. There have been many efforts to evaluate the prognostic factor visual recovery. Optical coherence tomography is a recently developed optical imaging technique that measures cross-sectional retinal thickness and is a useful diagnostic modality to assess optic nerve condition. The retinal nerve fiber layer on optical coherence tomography would seem to be the most reliable prognostic factor to date.¹² The thinner the retinal nerve fiber layer at diagnosis, the greater the optic atrophy and the greater the expected visual defect after treatment.^{12,13} Visual evoked potential is an electrophysiological response to visual stimulation, which can confirm the conductance of the optic nerve and is potentially associated with poor outcome of visual function.¹⁴ However, more accurate and stable waveform correction is required. In addition, electrophysiological assessment regarding electroretinography of RGCs is ongoing.¹²

One of the most notable findings of this study is that tumors with cavernous sinus invasion are an independent

TABLE 2. Characteristics of patients who were eventually discharged after observation during follow-up periods

Case No.	Sex	Age (yrs)	Initial Symptom	Initial Tumor Diam (mm)	Interval from Dx to End Obs (mos)	CS Invasion	Tumor Growth	Visual Det (VFD)	Endocrine		Surgical Outcome	Postop Complication
									Det	EOR		
1	M	56	HA, decreased vision	26	20	Yes	Yes	Bilat superior temporal quadrantanopia	No	GTR	Normal visual field	None
2	M	50	HA	36	14	Yes	Yes	Rt temporal hemianopia	No	GTR	Normal visual field	None
3	F	54	HA	26	53	Yes	Yes	Rt temporal hemianopia	No	GTR	Normal visual field	None
4	M	65	None	18	68	Yes	Yes	Bilat superior temporal quadrantanopia	No	GTR	Normal visual field	None
5	M	36	None	25	61	Yes	Yes	Bitemporal hemianopia	No	STR	Normal visual field	None
6	F	71	None	27	63	Yes	Yes	Bitemporal hemianopia	No	STR	Normal visual field	None
7	M	61	None	20	38	Yes	Yes	Bilat superior temporal quadrantanopia	No	GTR	Normal visual field	None
8	F	70	HA, blurred vision	25	81	Yes	Yes	Bilat superior temporal quadrantanopia	No	GTR	Nearly normal (bilat depression)	None
9	F	67	None	20	74	Yes	Yes	Bitemporal hemianopia	No	GTR	Normal visual field	None
10	M	55	None	16	18	Yes	Yes	Bilat superior temporal quadrantanopia	No	NA	Follow-up loss	NA
11	F	57	HA	15	55	No	Yes	Bitemporal depression	No	GTR	Normal visual field	None
12	F	55	None	29	60	No	Yes	Bitemporal hemianopia	No	GTR	Normal visual field	None
13	M	58	None	23	70	No	Yes	Bitemporal hemianopia	No	GTR	Normal visual field	Transient DI
14	M	72	None	20	32	No	No	Bilat superior temporal quadrantanopia	No	NA	Refused surgery	NA
15	M	52	None	30	35	Yes	No	Normal visual field	Yes	GTR	Function recovery	None
16	M	50	None	19	62	Yes	Yes	Normal visual field	Yes	GTR	Function recovery	None

DI = diabetes insipidus; diam = diameter; EOR = extent of resection; HA = headache; Obs = observation; STR = subtotal removal.

FIG. 3. Cox regression analysis revealed that initial cavernous sinus invasion was an independent risk factor for eventual treatment (HR 4.985, $p = 0.006$). Figure is available in color online only.

factor for visual deterioration, although further analysis revealed that the grade of cavernous sinus invasion by Knosp classification was not associated with visual deterioration. More macroadenomas than microadenomas had cavernous sinus invasion (29.6% vs 0%),⁴ and in our series its incidence was approximately 44.4%. Cavernous sinus invasion might be associated with tumor growth, but future studies with a large sample size and long-term follow-up can uncover some further associations. Tumors with cavernous sinus invasion should be carefully monitored.

There are some limitations in the present study, including its relatively small sample size to draw a concrete guideline. In addition, due to the retrospective design, there may be a selection bias. The studies such as hormone tests, ophthalmological evaluations, and MRI were not always performed under the same protocol in all patients. There were no objective examinations for optic nerve conditions to assess mass effects. The follow-up period was not long enough to evaluate the outcome of NFPA for more than 10 years.

However, our study showed that asymptomatic NFPA with optic nerve compression demonstrated more indolent behavior than expected. Importantly, this study does not guarantee that those tumors would be managed with the “wait-and-see” policy. The decision should be very carefully made, and it should be preceded by thorough discussion with patients and guardians. Although benign in nature, these tumors need individualized treatment and lifelong radiological and endocrinological follow-up. However, these findings, even though analyzed in rare cases, add to the literature, and this kind of effort has not

previously been attempted. Future studies are needed for more prospective and long-term analyses.

Conclusions

Asymptomatic NFPA with optic nerve compression can be conservatively managed at first. Careful selection of patients for surgical intervention with regular MRI and visual field test follow-up is a feasible option. Tumors with cavernous sinus invasion are candidates for early intervention.

Acknowledgments

This study is supported by a grant (no. H116C-1111-020016) to Y. H. Kim from the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea; and a grant (no. NRF-2017R1A2B2008412) to Y. H. Kim from the National Research Foundation of Korea by the Ministry of Science, ICT, and Future Planning (MSIP) of Korea.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Han, YH Kim. Acquisition of data: K Hwang, JH Kim, Lee, Yang, JM Hwang, CY Kim. Analysis and interpretation of data: K Hwang, YH Kim. Drafting the article: K Hwang. Reviewed submitted version of manuscript: Han, YH Kim. Statistical analysis: K Hwang. Administrative/technical/material support: YH Kim, Lee. Study supervision: Han.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Fig. 1. <https://thejns.org/doi/suppl/10.3171/2020.4.JNS192778>.

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