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Characteristics and clinical outcomes in pituitary incidentalomas and non-incidental pituitary tumors treated with endoscopic transsphenoidal surgery

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Abstract

Purpose: In this retrospective study, we investigated the status and validity of endoscopic transsphenoidal surgery (eTSS) for pituitary incidentalomas (PIs) as well as the value of basing the indication for surgery on the PI guidelines.

Methods: Patients who underwent eTSS at Fukuoka University Chikushi Hospital between 2012 and 2018 were divided into the PI group and the non-PI group in accordance with the PI guideline of the Endocrine Society and their clinicopathological characteristics and outcomes were compared and analyzed.

Results: A total of 59 patients were enrolled, with 35 patients in the PI group and 24 patients in the non-PI group. The diagnoses in the PI group were of non-functioning pituitary adenoma (NFPA) (n = 12, 34%), gonadotropin-producing pituitary adenoma (n = 8, 23%), Rathke cleft cyst (n = 7, 20%), meningioma (n = 4, 11%), and growth hormone-producing pituitary adenoma (n = 3, 9%); those in the non-PI group were of NFPA (n = 6, 25%), gonadotropin-producing pituitary adenoma (n = 3, 13%), Rathke cleft cyst (n = 3, 13%), growth hormone-producing pituitary adenoma (n = 3, 13%), and prolactin producing pituitary adenoma (n = 3, 13%). Regarding the preoperative factors, 1 patient in the PI group with panhypopituitarism was diagnosed with pituitary apoplexy (pure infarction) of an NFPA. The rates of postoperative anterior pituitary hormonal deficiencies (14% vs 46%, $P = .015$), residual tumor size (2 ± 5 vs 6 ± 7 mm, $P = .008$), and reoperation (n = 0, 0% vs n = 5, 21%, $P = .005$) were significantly different between the PI and non-PI groups.

Conclusions: This study showed that, postoperatively, the incidence of anterior pituitary hormonal deficiencies was lower in the PI than in the non-PI group, although it was comparable between the 2 groups before the operation. The patients in the PI group also had smaller residual tumors and a lower risk of reoperation than those in non-PI group. PIs could have a better postoperative clinical outcome than non-PIs when the indication for eTSS is based on preoperative scrutiny according to the PI guidelines and eTSS is performed by an experienced pituitary surgeon. Hence, more aggressive scrutiny and treatment for PIs might be desirable.

Abbreviations: CSF = cerebrospinal fluid, DI = diabetes insipidus, eTSS = endoscopic transsphenoidal surgery, GH = growth hormone, LAH = lymphocytic adenohypophysitis, NFPA = non-functioning pituitary adenoma, PI = pituitary incidentaloma, RCC = Rathke cleft cyst.

Keywords: clinical outcomes, endoscopic transsphenoidal surgery, non-functioning pituitary adenoma, patient characteristics, pituitary incidentalomas

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1. Introduction

A pituitary incidentaloma (PI) is a previously unsuspected pituitary lesion that is discovered during an imaging study typically performed for an unrelated reason.[1–4] Imaging is usually performed to evaluate headaches, neurological or central nervous system complaints, and head or neck trauma, which are not initially indicative of PIs. Symptoms related to PIs include vision loss, clinical manifestation of hypopituitarism, or excess hormone secretion. The Endocrine Society (Washington, DC) produces guidelines for the clinical management of several endocrine diseases including PIs, which define PIs as tumors of the pituitary gland discovered incidentally on imaging performed to explore symptoms not specifically related to the lesion (e.g., visual loss) or a clinical manifestation of hormonal disorders. This guideline also notes that PIs include pituitary adenomas, Rathke cleft cysts (RCC), benign tumors except pituitary adenomas (e.g., craniopharyngioma, meningioma), and malignant tumors located in the pituitary gland.[5] By convention, micro-incidentalomas measure less than 1 cm and macro-incidentalomas are at least 1 cm in size.

The widespread application of sensitive brain imaging techniques, such as computed tomography and magnetic resonance imaging, has increased PI diagnosis.[1,6–9] Although the etiology of PIs covers various pathologies, approximately 90% of PIs are benign adenomas, and such lesions may cause visual and/or neurological abnormalities.[5] The guidelines by the Endocrine Society recommend that patients with PIs should undergo thorough medical history-taking and a complete physical examination, including of evidence of asymptomatic hormonal disorders.[1,5] Some PIs, such as functional adenomas and other surgically indicated tumors, cannot be diagnosed without taking a medical history as well as physical and endocrinological examinations. However, it remains controversial whether preoperative scrutiny in full compliance with the guidelines for PI is thorough.[1,5] Based on a previous report, despite the existence of updated guidelines, in practice, surgical indications may be judged on the basis of tumor size alone, even if PIs are noted, especially if the clinician is not a pituitary surgery specialist.[6] To our knowledge, there have been no studies comparing PIs with non-PIs, especially including outcome of eTSS. The aim of this study is to investigate the actual status, validity of the surgical procedure, and PIs guideline's suitability of surgical indications for PIs by comparing the characteristics and clinical outcomes of PI and non-PI patients who underwent adequate medical history taking, physical examination, and perioperative endocrinological scrutiny and eTSS in accordance with guidelines of the Endocrine Society at a single center.

2. Methods

2.1. Design, participants, ethical considerations, and data collection

This was a retrospective study of patients who underwent eTSS at Fukuoka University Chikushi Hospital, Japan, between 2012 and 2018. The indication for eTSS in PIs was in accordance with the aforementioned guidelines by the Endocrine Society,[5] while in non-PIs, it was for symptomatic tumors or functional pituitary adenomas. All patients underwent a thorough medical history and physical and clinical examination. Regarding preoperative and postoperative endocrinological investigations, all patients were hospitalized and underwent endocrinological hormone blood sampling tests including loading tests before and 1 month after surgery. In addition, all patients also underwent postoperative endocrinological evaluations at the last follow-up or 12 months after surgery. The patients provided written informed consent before participating in the study, and the study design was approved by the relevant institutional review board (approval no. R19–004).

In accordance with Freda guidelines by the Endocrine Society,[5] all patients underwent adequate medical history taking and physical examination, including evaluations for hypopituitarism and hormone hypersecretion syndrome. Patients with evidence of either of these conditions underwent appropriate hormone loading tests.

2.2. Surgical technique

eTSS was performed by experienced pituitary surgeons. Our surgical technique was based on a bilateral nostril approach as previously reported.[10] As cerebrospinal fluid (CSF) leakage is often encountered during eTSS, it is important to repair the sella turcica and skull base to prevent this. In cases where CSF leakage may occur during surgery, such as in the anterior extended approach for tuberculum sellae meningiomas, a pedicle mucosal flap is prepared beforehand and placed on 1 side of the nasal cavity.[11] If an unexpected increase in CSF leakage occurs, the flap can also be placed on 1 side of the nasal septum mucosa during the repair. The mucous membrane around the sphenoid sinus is maintained to the maximum extent possible. If the pedicle mucosal flap cannot be used during reoperation, leakage can be prevented by collecting femoral fascia tissue, squeezing it to the bottom of the sellae and skull base, and covering the exposed skull widely.[12] The fat is initially used to close the cavity so that it adheres to the dura from the inner surface.[13] Furthermore, the leakage is covered with a polyglycolic acid sheet (Neoveil), and the material is attached to the dura mater and the fat using fibrin glue spray (Bolheal).[14] A large pedicle mucosal flap is placed over this area and fastened by squeezing with a balloon catheter (Sinus Balloon Catheter, Fuji Systems Co., Ltd., Tokyo, Japan).[15] At this point, it is important for the pedicle mucosal flap to closely adhere to the open end of the bottom of the sellae and skull base. Care should be taken, as unexpected CSF leakage can occur if gaps are formed. Lumbar drainage is normally not used in combination with this procedure, while it may be inserted postoperatively when deemed necessary.

2.3. Definitions of variables of interest

The patients were divided into the PI group and non-PI (other tumors) group in accordance with the guidelines of the Endocrine Society.[1,5] For example, the patients who underwent imaging mainly due to headache were included in the PI group, while those who underwent imaging for vision loss were included in the non-PI group. Pituitary tumors were classified as follows: adrenocorticotropic hormone-producing pituitary adenoma, craniopharyngioma, gonadotropin-producing pituitary adenoma, growth hormone (GH)-producing (somatotroph) pituitary adenoma, lymphocytic adenohypophysis (LAH), non-functioning pituitary adenoma (NFPA), prolactin-producing pituitary adenoma, RCC, meningioma, and metastasis as previously reported.

Hormone-producing pituitary adenomas were diagnosed both endocrinologically and pathologically. The diagnosis of hormone-producing pituitary adenomas was performed as previously described.[1] Postoperative evaluations for improvement of each excess pituitary hormone level were performed endocrinologically both 1 month after surgery and at the last follow-up visit or 12 months following surgery.

Preoperatively, 1 or more anterior pituitary hormonal deficiencies were considered. Postoperative anterior pituitary hormonal deficiencies were defined as unresolved anterior pituitary hormonal deficiencies both 1 month after surgery and at the last follow-up visit or 12 months following surgery. The diagnosis of anterior pituitary hormonal deficiencies was performed as previously described.[1] Preoperative diabetes insipidus (DI) was diagnosed clinically and endocrinologically. Postoperative DI was defined as permanent DI both 1 month after surgery and at the last follow-up or 12 months after surgery. The diagnosis of DI was performed as previously described.[1]

2.4. Statistical analysis

The following patient characteristics were compared between the PI and non-PI groups: sex, medical history, chief complaint, type of tumor (microadenoma or macroadenoma), pathology, preoperative tumor size, preoperative suprasellar progression evaluated using magnetic resonance imaging findings, preoperative endocrine findings, eTSS findings, and clinical outcomes, such as surgical complications, postoperative endocrine findings, postoperative residual tumor size, mortality rate, and the presence or absence of reoperation.

Continuous variables are expressed as median (internal quartile range), whereas categorical variables are expressed as percentages. Fisher exact test was used for categorical variables, whereas the Mann–Whitney *U* test was used for continuous variables.

A *P*-value of $< .05$ was considered statistically significant. The statistical analyses were conducted using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics

A total of 59 patients were enrolled (none of the patients were excluded); there were 35 patients in the PI group and 24 patients in the non-PI group.

Table 1 shows the comparison of patient characteristics between patients with PIs and non-PIs (other pituitary tumors) treated with eTSS. For all 59 patients, the age (mean ± SD) was 57 ± 17 years, and there were 24 (41%) men and 35 (59%) women; the follow-up duration was 29 ± 17 months, and the maximum tumor diameter was 22 ± 7.7 mm.

The proportion of patients who mainly underwent imaging for headaches was significantly higher in the PI group than in the non-PI group ($P = .02$). There was no significant difference in other factors (except for vision and visual field disturbances) between the PI group and the non-PI group. Regarding preoperative factors, 1 patient in the PI group with panhypopituitarism was diagnosed with pituitary apoplexy (pure infarction) of NFPA. In the non-PI group, 1 patient (4%) who

Table 1

Comparison of patient characteristics between patients with pituitary incidentalomas and other tumors treated with endoscopic transsphenoidal surgery.

Patient characteristics	Pituitary incidentaloma n = 35	Non-pituitary incidentaloma n = 24	*P* value
Age, (yr)	58 (49–68)	63 (51–70)	.257
Sex			
Male, n (%)	13 (37)	11 (46)	.593
Female, n (%)	22 (63)	13 (54)	
Past medical history			
Hypertension	11 (31)	9 (38)	.780
Diabetes mellitus	4 (11)	2 (8)	1
Dyslipidemia	0 (0)	7 (29)	1
Chief complaint			
Wobble, n (%)	4 (11)	0 (0)	.138
Vision and visual field disturbance, n (%)	0 (0)	11 (46)	<.001**
Headache, n (%)	13 (37)	2 (8)	.015*
Oculomotor palsy, n (%)	0 (0)	2 (8)	.161
Gynecological symptoms, n (%)	0 (0)	1 (4)	.407
Others, n (%)	18 (52)	7 (29)	.175
Follow-up duration, (mo)	23 (13–38)	31 (21–50)	.158
Tumor type			
Microadenoma (<10 mm)	0 (0)	2 (8)	.082
Macroadenoma (>10 mm)	35 (100)	22 (92)	
Tumor size (maximum diameter), (mm)	19 (17–23)	25 (20–31)	.077
Suprasellar progression, n (%)	27 (77)	18 (75)	1
Preoperative excess producing of hormones, n (%)	4 (11)	7 (29)	.102
Preoperative anterior pituitary hormonal deficiencies, n (%)	16 (46)	16 (67)	.183
Preoperative diabetes insipidus, n (%)	0 (0)	1 (4)	.407

Data are shown as the median (internal quartile range (IQR)).
* $P < .05$.
** $P < .001$.

had preoperative DI eventually developed metastatic cancer (Fisher test, $P=.02$, data not shown).

3.2. Comparison of pathological diagnosis

Table 2 shows the comparison of pathological diagnoses between patients with PIs and non-PIs (other tumors) treated with eTSS. The diagnoses (n=59) included adrenocorticotropic hormone producing pituitary adenoma (2, 3.4%), craniopharyngioma (n=1, 1.7%), gonadotropin producing pituitary adenoma (n=11, 19%), GH producing (somatotroph) pituitary adenoma (n=6, 10%), LAH (n=1, 1.7%), NFPA (n=18, 31%), PRL producing pituitary adenoma (n=3, 5.1%), RCC (n=10, 17%), meningioma (n=6, 10%), and metastasis (n=1, 1.7%).

The most common diagnosis in the PI group (n=35) was NFPA (n=12, 34%), followed by gonadotropin-producing pituitary adenoma (n=8, 23%), RCC (n=7, 20%), meningioma (n=4, 11%), GH-producing (somatotroph) pituitary adenoma (n=3, 9%), and LAH (n=1, 3%). In the PI group, functioning pituitary adenomas were found in 11 cases (31%). In the non-PI group, the diagnoses were NFPA (n=6, 25%), gonadotropin-producing pituitary adenoma (n=3, 13%), RCC (n=3, 13%), GH-producing (somatotroph) pituitary adenoma (n=3, 13%), PRL producing pituitary adenoma (n=3, 13%), meningioma (n=2, 8%), craniopharyngioma (n=1, 4%), and metastasis (n=1, 4%). There were no significant differences in the pathological diagnoses between patients in PI group and non-PI group.

3.3. Comparison of clinical characteristics

Table 3 shows the comparison of patient clinical outcomes between patients with PIs and non-PIs (other tumors) treated with eTSS. The PI group had a lower rate of postoperative anterior pituitary hormonal deficiencies (14% [n=5] vs 46% [n=11], $P=.015$), smaller residual tumor size (mean ± SD; 2 ± 5 vs 6 ± 7 mm, $P=.008$), and a lower risk rate of reoperation (0% [n=0] vs 21% [n=5], $P=.005$). Regarding the postoperative factors, CSF leakage in the PI group was not confirmed in any case (0%). Moreover, in 2 cases (6%) in the PI group, postoperative panhypopituitarism (pituitary apoplexy and secondary hypophysitis) was observed; these denote NFPA and are associated with RCC rupture (data not shown).

For all 5 reoperation cases, while none was confirmed in the PI group, 5 patients (2 with NFPA, 2 with RCC, and 1 with gonadotropin-producing pituitary adenoma) in the non-PI group underwent re-extraction or cyst fenestration for all recurrences.

4. Discussion

As a whole, in our study, the most common diagnosis in the PI group was of NFPA, followed by gonadotropin-producing pituitary adenoma. In the PI group, functioning pituitary adenomas were found in 11 cases. Interestingly, somatotroph adenomas were found in 3 cases in the PI group. The rates of postoperative anterior pituitary hormonal deficiencies, residual tumor, and reoperation were significantly different between the PI group and non-PI group.

Regarding the postoperative symptoms of patients, headache as a common chief complaint was significantly more frequent in the PI than in the non-PI group, which agrees with the findings of a previous study.[16] This might be due to selection bias in defining PIs when the imaging shows a pituitary tumor triggered by a headache.

The widespread use of advanced imaging techniques has led to increased diagnosis of PIs.[1,7–9] PIs are more prevalent than macroadenomas, with the average worldwide prevalence of PIs being 10%, while that of macroadenomas (>10 mm) is reported to be less than 1%.[17] The most frequently encountered lesions were NFPAs, followed by gonadotropin-producing pituitary adenomas. This result partially differs from that of another study.[17] The observed controversy might have been caused by equipment limitations to perform gonadotropin immunostaining in some centers. We performed immunostaining for gonadotropin against all tumor samples of our patients, which could have led to the accurate diagnosis of gonadotropin-producing pituitary adenoma, attributed to cases that would otherwise be considered clinical NFPAs.

In the PI group, functioning pituitary adenomas were found in 11 cases (31%). Moreover somatotroph adenomas were found in three cases (9%). Esteves et al[16] reported only 1 case of somatotroph adenoma (1.4%) among 71 PI cases. Somatotroph adenoma is a key factor in PI, as it influences prognosis, early diagnosis, and treatment, while acromegaly is characterized by a broad range of manifestations.[18] Early diagnosis is important to treatment success but is often delayed as the symptomatology

Table 2

Comparison of pathological diagnosis between patients with pituitary incidentalomas and other tumors treated with endoscopic transsphenoidal surgery.

Pathological diagnosis	Pituitary incidentaloma n=35	Non-pituitary incidentaloma n=24	*P* value
ACTH producing pituitary adenoma, n (%)	0 (0)	2 (0)	.161
Craniopharyngioma, n (%)	0 (0)	1 (4)	.407
Gonadotropin producing pituitary adenoma, n (%)	8 (23)	3 (13)	.498
GH producing pituitary adenoma, n (%)	3 (9)	3 (13)	.679
LAH, n (%)	1 (3)	0 (0)	1
NFPA, n (%)	12 (34)	6 (25)	.568
PRL producing pituitary adenoma, n (%)	0 (0)	3 (13)	.062
RCC, n (%)	7 (20)	3 (13)	.506
Meningioma, n (%)	4 (11)	2 (8)	1
Metastasis, n (%)	0 (0)	1 (4)	.407

ACTH=adrenocorticotropic hormone, GH=growth hormonea, LAH=lymphocytic adenohypophysitis, NFPA=non-functioning pituitary adenoma, PRL=prolactin, RCC=Rathke cleft cyst.
*$P<.05$.
**$P<.01$.

Table 3

Comparison of patient clinical outcomes between patients with pituitary incidentalomas and other tumors treated with endoscopic transsphenoidal surgery.

Patient clinical outcomes	Pituitary incidentaloma n = 35	Non-pituitary incidentaloma n = 24	*P* value
Intraoperative cerebrospinal fluid leak	13 (37)	10 (42)	.790
Use of a pedicled mucosal flap	9 (26)	4 (17)	.529
Postoperative cerebrospinal fluid leak	0 (0)	1 (4)	.223
Postoperative diabetes insipidus	2 (6)	3 (16)	.388
Postoperative meningitis	1 (3)	1 (4)	1
Postoperative epistaxis	1 (3)	1 (4)	1
Postoperative anterior pituitary hormonal deficiencies	5 (14)	11 (46)	.0150*
Postoperative excess producing of hormones	0 (0)	0 (0)	1
Residual tumor size (maximum diameter), (mm)	0 (0–0), 2 ± 5 (mean ± SD)	0 (0–11), 6 ± 7 (mean ± SD)	.008**
Reoperation	0 (0)	5 (21)	.005**
Mortality rate	0 (0)	0 (0)	1

Data are shown as the median (internal quartile range (IQR)).
* $P < .05$.
** $P < .01$.

overlaps with that of common disorders. In our study, no patients with somatotroph adenoma had specific symptoms of acromegaly, such as morphologic manifestations, snoring syndrome, asthenia, enlarged hands and feet, hypertension, and carpal/cubital tunnel syndrome. It is possible that a PI may result in acromegaly without obvious symptoms, suggesting the importance of thorough endocrinological scrutiny.

In our study, 1 patient in the PI group with preoperative panhypopituitarism was diagnosed with pituitary apoplexy of NFPA. Even for patients with PIs, a preoperative endocrine test must be paramount, as panhypopituitarism could occur before eTSS. However, in our study, there was no significant difference in the frequency of preoperative anterior pituitary hormonal deficiencies between the patients in the PI group and those in the non-PI group. Kitano and Taneda[12] highlighted the importance of preoperative evaluation of endocrine function in relation to the surgical indications of PI.[12] Although hypopituitarism is more frequent in larger lesions, it can also occur in microadenomas (<10 mm). The incidence of malignancy is higher in macroadenomas and solid lesions than in microadenomas and cystic lesions. The baseline evaluation should thus include complete medical history taking and physical examination, screening for hormone hypersecretion and hypopituitarism, and visual field examination if the lesion is abutting the optic nerves or chiasm.[17]

Furthermore, in our study, the incidence of postoperative anterior pituitary hormonal deficiencies, residual tumor size, and reoperation rate were significantly different between the PI and non-PI groups, which might indicate that the gland is effectively decompressed in PIs, as evidenced by the lower risk of postoperative anterior pituitary hormonal deficiencies in the PI group than in the non-PI group. The preoperative tumor size (maximum diameter) in the PI group was 19 (17–23) mm. In previous reported PI cases,[2,3,6] the tumor was ≤2 cm and not in contact with the chiasm, and surgery was not indicated for NFPAs. However, thorough scrutiny for guideline compliance is desirable because PIs could be distinguished from functional adenomas and other surgically indicated tumors based not only on tumor size but also on basic hormonal values and stress test results.[9]

Our study also revealed that eTSS for PIs performed by experienced pituitary surgeons led to good clinical outcomes with low complication rates. A previous study limited to incidentally detected NFPA indicated that tumors without visual loss or hormonal deficiencies might have better outcome than those with visual loss or hormonal deficiencies,[19] while no previous studies have examined pituitary incidentalomas as a whole. Furthermore, there were no studies all patients were performed eTSS. In our study, although there were no differences about tumor size and the incidence of anterior pituitary hormonal deficiencies between the PI-group and non-PI group, patients in the PI-group had significantly better outcomes than those of the non-PI group. Rutkowski et al[20] developed an objective 5-point grading scale for PA consistency based on intraoperative characteristics, including ease of tumor debulking, manipulation, and instrument selection, ranging from cystic/hemorrhagic tumors (grade 1) to calcified tumors (grade 5). In the study, high-grade PAs had more preoperative and postoperative panhypopituitarism. Patients with preoperative visual dysfunction experienced greater improvement in low-grade PAs. Besides, gross-total resection was more likely with lower PA consistency score. These might explain the results of our study; the PI group might contain more cases with lower-grade PA consistency than the non-PI group. It is also possible that there was less adhesion to the surrounding neurovascular structures in the PI group, especially in cases of pituitary adenomas, which were more likely to be extracapsularly removed, than in the non-PI group, and there was a case of craniopharyngioma in the non-PI group, which is more likely to recur and cause endocrine dysfunction, and 1 of metastasis, which has a worse prognosis. In addition, we should keep in mind that not all lesions will be amenable to treatment using the endoscopic endonasal technique. The choice of the proper technique requires a thorough knowledge of the surgical anatomy, biological behavior character of the disease, patient risk factors, and possible complications that can occur after these procedures and are not particularly associated with the neuropathology. The most common complication, CSF leakage, can be successfully prevented via surgical techniques with pedicled nasoseptal flap and multi-layered closure, and our operative management was effective in almost all patients in the PI group. Lumbar CSF drainage may be placed postoperatively in all cases of high-risk CSF leakage to reduce the CSF pressure and allow healing of the reconstruction. The insertion of a postoperative lumbar drainage may be controversial; however,

the possibility of reducing the pressure of the CSF on the reconstruction, especially during the first 72 postoperative hours favors the healing process.[21] It may be worth considering preoperative lumbar drainage, depending on the risk of CSF leakage.

Our study has a limitation; it was based on a survey performed with a limited number of patients. Future prospective studies with a larger number of cases should be performed to confirm the present findings.

To conclude, this study showed that, postoperatively, the incidence of anterior pituitary hormonal deficiencies was lower in the PI than in the non-PI group, although it was comparable between the 2 groups before the operation. The patients in the PI group also had smaller residual tumors and a lower risk of reoperation than those in non-PI group. PIs could have a better postoperative clinical outcome than non-PIs when the indication for eTSS is based on preoperative scrutiny according to the PI guidelines and eTSS is performed by an experienced pituitary surgeon. Hence, more aggressive scrutiny and treatment for PIs might be desirable.

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