**Presentation and surgical results of incidentally discovered nonfunctioning pituitary adenomas: evidence for a better outcome independently of other patients' characteristics**

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**Abstract**

**Objective:** Few data are available on the surgical results in patients with incidentally discovered nonfunctioning pituitary adenoma (NFPA). We investigated the efficacy and safety of surgery in patients with incidentally discovered NFPA.

**Design:** Retrospective analysis of prospectively recorded outcomes.

**Methods:** From 1990 to 2011, of 804 consecutive patients undergoing surgery for NFPA, 212 cases had an incidentally discovered tumor (26.4%). Among them, 117 patients were asymptomatic, while 95 had some visual and/or hormonal deficit. The main outcome of the study was to evaluate the frequency of radical resection as judged on the first postoperative neuroimaging study and detection of recurring disease during long-term follow-up.

**Results:** Postoperative residual tumor was detected in 8.9% of patients with asymptomatic incidentalomas as compared with 31.2% of patients with symptomatic incidentalomas ($P < 0.001$) and 41.2% of patients in the control group ($P < 0.001$). Multivariate analysis confirmed that having an asymptomatic incidentaloma was independently associated with a better outcome. The 5-year recurrence-free survival in patients with incidentaloma was 86.8% (95% CI 80.2–92.4%) as compared with 77.9% (95% CI 73.6–82.2%; $P < 0.01$) in the control group. This difference was almost completely due to a lower frequency of relapse in asymptomatic patients. Multivariate analysis confirmed the independent lower risk of tumor recurrence in asymptomatic NFPA.

**Conclusion:** Our study shows for the first time that surgically treated patients with asymptomatic NFPA have a better early and long-term outcome that is independent from all the other demographic, clinical, and morphologic characteristics of the patients.

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**Introduction**

Nonfunctioning pituitary adenomas (NFPA) are a heterogeneous group of tumors that include null-cell adenomas, oncocytomas, gonadotropin-secreting adenomas, and silent adrenocorticotropin, growth hormone, prolactin (PRL), and thyrotropin (TSH) adenomas. NFPA represent 25–30% of all pituitary adenomas (1). The annual incidence is 4–5 cases per million people with an estimated worldwide prevalence of 50–60 cases per million people. No relevant differences in therapy and prognosis for the various subtypes of NFPA have consistently been described (2). As they are not associated with hormonal hypersecretion, NFPA are often undiagnosed until they grow enough to compress adjacent anatomical structures and cause visual disturbances and/or impaired pituitary function. However, more patients are diagnosed because of an imaging study performed for unrelated reasons, the so-called pituitary incidentaloma. The definition of pituitary incidentaloma varies among authors: some include only lesions that satisfy radiographic criteria for pituitary adenoma (3, 4), whereas others include all sellar lesion (5, 6, 7, 8, 9, 10). Pooling the data of 18 902 subjects in a meta-analysis, Molitch (11) reported that the frequency of pituitary adenomas found at autopsy in subjects with no ante-mortem history of pituitary diseases was 10.7% (range, 1.5–31%), but almost all tumors were tiny microadenomas. In keeping with the autopic data, pituitary lesions larger than 10 mm in diameter have been described in only 0.2% of 3550 subjects who underwent computed tomography scan for headache or changes in mental status (12). Similarly, only 0.16–0.3% of normal subjects evaluated by
magnetic resonance imaging (MRI) had evidence of a pituitary lesion larger than 10 mm (13, 14).

Despite the high prevalence of pituitary incidentalomas, experts remain uncertain about the optimal therapeutic approach to such cases. In all patients with incidentally discovered NFP A who have either visual or neurological abnormalities, the Endocrine Society guidelines suggest transsphenoidal surgery as first-line therapy (15). Surgery is usually advised also in asymptomatic patients with tumors that abut the optic chiasm (15). In older patients without visual deficit, a more conservative approach might be preferred (16, 17). Even in patients with asymptomatic NFP A, immediate surgery might be considered, but most authors recommend clinical and neuroradiological follow-up as first option (15, 18, 19). However, these recommendations are not based on hard evidence because large and comparative studies on this topic are lacking.

The aims of this study are to report the efficacy and safety of surgery in a large series of patients with incidentally discovered NFP A, further distinguishing truly asymptomatic from symptomatic tumors.

Subjects and methods

Patients

From 1990 to 2011, 957 consecutive patients underwent surgical resection of NFP A at the Department of Neurosurgery of the Università Vita-Salute of Milan. All surgical procedures have been performed by two experienced and dedicated neurosurgeons using a standard microsurgical technique (20). The diagnosis of NFP A was based on the clinical and biochemical absence of hormone hypersecretion and the histopathological confirmation of a pituitary adenoma. After exclusion of 153 patients who had previously undergone pituitary surgery in other hospitals, 804 patients were included in the study. No patient had previously received radiation therapy. Surgical results of 491 patients operated upon from 1990 to 2005 were reported previously (2).

Age at surgery, sex, symptoms at presentation, reason to perform neuroimaging, reason to undergo surgery, hormonal data, and complications of surgery were prospectively collected. Reasons to undergo surgery were grouped into two categories: demonstration of growth of the pituitary lesion in patients initially choosing neuroimaging follow-up or preference by the patient’s endocrinologist. According to the literature (15), NFP A incidentalomas were defined as those tumors that were detected by imaging studies performed for symptoms, signs, and/or reasons unrelated to the hypothalamic/pituitary region, with the possible exception of headache. After a thorough endocrinological and ophthalmologic examination, incidentalomas were further subdivided into asymptomatic and symptomatic tumors according to the absence or presence, respectively, of clinical and biochemical signs of hypopituitarism and/or visual disturbances. Postmenopausal women with inappropriately low or normal gonadotropin levels, which are considered clinically irrelevant in this context, were not considered to have hypogonadism.

Standard informed consent was obtained from each patient undergoing pituitary surgery.

Preoperative evaluation

All patients underwent baseline hormonal, neuro-ophthalmological, and neuroradiological evaluation before surgery, as previously described (2). Secondary hypothyroidism was diagnosed by the presence of low free thyroxine with normal or low TSH level. Secondary adrenal insufficiency was diagnosed in patients with morning cortisol level below 50 ng/ml or morning cortisol levels between 50 and 120 ng/ml and clinical symptoms of adrenal insufficiency that improved with glucocorticoid replacement therapy. Hypogonadotropic hypogonadism was diagnosed in premenopausal women with oligomenorrhea or amenorrhea and in adult males with subnormal testosterone levels. Low or normal gonadotropin levels were also required in both sexes. Hyperprolactinemia was defined as PRL levels > 20 µg/l in women and 15 µg/l in men in the absence of dopaminergic therapy. Visual field defect were detected by standard automated perimetry techniques.

Neuroradiological examination of the sellar region was performed whenever possible by MRI. Tumors were considered invasive of the cavernous sinus if they corresponded to grade 3 or 4 in the classification of Knosp et al. (21). Tumors intraoperatively noted to interrupt the sellar floor were considered invasive of the sphenoid sinus (2).

Postoperative evaluation

Endocrinological, ophthalmological, and neuroradiological examinations took place 2–6 months after surgery. Based on the first postoperative study – always MRI except when contraindicated – patients were subdivided into two groups: (i) patients with tumor remnants; and (ii) patients without any sure evidence of tumor remnants.

According to subsequent imaging studies advised at 1-year intervals for 2–3 years and then at longer intervals, patients were defined as having recurrence of disease if the pathological tissue was not detected before or growth of tumor remnants already known to exist on the previous examination appeared (2).

The follow-up information was collected during ambulatory control visits or by telephonic contact with patients or their physician.
Statistical analysis

Continuous data were examined for homogeneity of variance and are expressed as means ± s.e.m. Differences between two groups were tested for significance using the unpaired Student’s t-test. ANOVA was used to compare more than two groups, and Bonferroni’s adjustment was used to adjust for multiple testing in post hoc comparisons. \( \chi^2 \) tabulation with Yates correction or Fisher exact test was used to compare binomial proportions, as appropriate. Multiple logistic regression analysis with the resulting odds ratio (OR) was used to determine which variables independently predicted absence of residual tumor at the first postoperative neuroimaging study. The cumulative risk of the development of tumor recurrence was calculated according to the Kaplan–Meier method and the log rank-test. Recurrence-free survival was measured from the date of surgery to the date of tumor recurrence. Patients were censored at the date of the last neuroimaging follow-up. With the use of proportional-hazard analysis, hazard ratio (HR) and 95% CI were generated for the association between baseline characteristics and tumor recurrence.

A two-tailed probability value < 0.05 was considered to indicate statistical significance. All calculations were performed using the statistical package Stat View 5.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Two-hundred and twelve patients had an incidentally discovered tumor, representing 26.4% of the study sample. One-hundred and seventeen patients (14.6%) had normal pituitary function and no visual defect (asymptomatic incidentalomas), whereas the remaining 95 patients (11.8%) constituted the group of symptomatic incidentalomas because preoperative evaluation showed isolated visual defects in 20 cases (21.1%), pituitary hormone deficiency exclusively in 44 cases (46.3%), and concomitant visual and pituitary defects in the remaining 31 cases (32.6%). Eleven postmenopausal women had isolated gonadotropin deficiency; but they were classified into the asymptomatic group because of the clinical irrelevance of the deficit. The reasons to perform a neuroimaging study are summarized in Table 1. The most frequent ones were headache (19.8%) and dizziness (14.6%). There were no significant differences between asymptomatic and symptomatic incidentalomas (Table 1), except for a slight excess of headache in asymptomatic incidentalomas \( (P=0.05) \) and stroke or transient ischemic attack in symptomatic incidentalomas \( (P=0.06) \). Demonstration of tumor growth was the reason for undergoing surgery in 19 (16.2%) and 16 patients (16.8%) in the asymptomatic and symptomatic incidentalomas respectively \( (P=NS) \). The control group consisted of the 592 patients whose NFPA was not discovered incidentally, including 71 patients (12.0%) who had pituitary apoplexy.

The main clinical characteristics of the study population are summarized in Table 2. As expected, patients with asymptomatic incidentalomas had smaller and less invasive tumors than either patients with symptomatic incidentalomas and patients in the control group. On the other hand, patients with symptomatic incidentalomas were older than patients in the control group, but had similar tumor size and invasiveness. In keeping with our recommendation to forgo treatment in patients with NFPA smaller than 1 cm, only three patients, who showed radiological growth of an incidentally discovered tumor, had microadenomas.

Early postoperative results

There was no perioperative death among patients with incidentalomas, while five patients in the control group died because of surgical complications. Severe adverse events occurred in four patients with asymptomatic incidentaloma (3.4%) as compared with five patients in symptomatic incidentalomas (5.3%; \( P=NS \)), while minor adverse events, such as cerebrospinal fluid leak not requiring surgical repair or transient hyponatremia, occurred in nine (7.7%) and nine patients (9.5%; \( P=NS \)) of the two groups respectively. Severe adverse events in the control group (9.3%) occurred more frequently than in patients with asymptomatic incidentaloma \( (P<0.05) \).

Worsening of pituitary function was analyzed for each axis separately (Table 3). Overall, hormonal deficits of new onset were uncommon. In particular, patients with asymptomatic incidentaloma experienced new onset of hypogonadism, hypothyroidism, hypoadrenalism, and diabetes insipidus in 5.2, 2.7, 5.3, and 6.8% of cases respectively.

Thirty-one patients did not perform a postoperative MRI (five patients with asymptomatic incidentalomas,

<table>
<thead>
<tr>
<th>Cause</th>
<th>Asymptomatic incidentalomas ( n=117 )</th>
<th>Symptomatic incidentalomas ( n=95 )</th>
<th>All ( n=212 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>29 (24.8%)</td>
<td>13 (13.7%)</td>
<td>42 (19.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (14.5%)</td>
<td>14 (14.7%)</td>
<td>31 (14.6%)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>6 (5.1%)</td>
<td>13 (13.7%)</td>
<td>19 (9.0%)</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>9 (7.7%)</td>
<td>8 (8.4%)</td>
<td>17 (8.0%)</td>
</tr>
<tr>
<td>Head or cervical trauma</td>
<td>9 (7.7%)</td>
<td>8 (8.4%)</td>
<td>17 (8.0%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (6.0%)</td>
<td>5 (5.3%)</td>
<td>12 (5.7%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>6 (5.1%)</td>
<td>5 (5.3%)</td>
<td>11 (5.2%)</td>
</tr>
<tr>
<td>Tumor staging</td>
<td>5 (4.3%)</td>
<td>5 (5.3%)</td>
<td>10 (4.7%)</td>
</tr>
<tr>
<td>Other causes</td>
<td>29 (24.8%)</td>
<td>24 (25.2%)</td>
<td>53 (25.0%)</td>
</tr>
</tbody>
</table>
two patients with symptomatic incidentalomas, and 24 control patients) because of loss to follow-up or refusal by the patient. Overall, tumor remnants occurred in 273 out of 773 cases available for analysis (35.3%). Ten of 112 (8.9%) patients with asymptomatic incidentalomas had evidence of residual disease on the first postoperative MRI, as compared with 29 of 93 (31.2%) patients with symptomatic incidentalomas (P < 0.001) and 234 of 568 (41.2%) patients in the control group (P < 0.001). The frequency of tumor remnants between symptomatic incidentalomas and the control group was not significant. We then performed a multivariate logistic regression analysis to verify which characteristics were independently associated with early surgical outcome. Two different models, including 742 patients with complete data sets each, were examined. In the first one, asymptomatic and symptomatic incidentalomas grouped together were compared against the patients in the control group. Postoperative persistence of tumor remnants was positively associated with extension into the cavernous sinus (OR 7.6; 95% CI 5.0–11.4; P < 0.001) and maximum tumor diameter (OR 1.11 per unit increase; 95% CI 1.08–1.14; P < 0.001), while it was negatively associated with tumor apoplexy (OR 0.17; 95% CI 0.07–0.40; P < 0.001) and classification as incidentalomas (OR 0.46; 95% CI 0.28–0.76; P < 0.01). Other characteristics, such as sex, patient’s age, year of surgery, and extension into the sphenoid sinus had no significant effect on surgical outcome. In the second model, we compared asymptomatic incidentalomas against symptomatic incidentalomas plus the control group. Again, extension into the cavernous sinus (OR 7.4; 95% CI 4.9–11.2; P < 0.001) and maximum tumor diameter (OR, 1.11 per unit increase; 95% CI 1.08–1.14; P < 0.001) were associated with persistence of tumor residue after surgery, while tumor apoplexy at diagnosis (OR 0.19; 95% CI 0.08–0.43; P < 0.001) and asymptomatic incidentalomas (OR 0.32; 95% CI 0.15–0.68; P < 0.01) were associated with absence of tumor remnants. Reclassification of the 11 postmenopausal women with gonadotropin deficiency from the asymptomatic to the symptomatic group did not significantly change the results.

**Tumor recurrence**

According to our definition of tumor recurrence (see above), 689 patients (85.7%) with at least two postoperative neuroimaging studies were available for further analyses. Ninety-three patients had an asymptomatic incidentaloma, 84 had a symptomatic incidentaloma, and the remaining 512 patients were in the control group. The median follow-up period was 8.7 ± 2 years. Overall, relapse of NFPA occurred during follow-up in 156 of 689 patients (22.6%). The risk of tumor recurrence was lower in patients with incidentalomas than in the control group (Fig. 1). The 5-year recurrence-free survival in patients with incidentalomas was 86.8% (95% CI 80.2–92.4%) as compared with 77.9% (95% CI 73.6–82.2%; P < 0.01; Fig. 1) in the control group. However, this difference was almost completely driven by the disparity between patients with asymptomatic and symptomatic incidentalomas (Fig. 2). The 5-year recurrence-free survival in patients with asymptomatic incidentalomas was 96.7% (95% CI 92.0–100%) as compared with 77.0% (95% CI 65.3–88.7%; P < 0.01; Fig. 2) in symptomatic incidentalomas.

Multivariate Cox analysis showed that the risk of tumor recurrence was positively associated with the presence of postoperative tumor remnants (HR 5.0; 95% CI 3.6–7.1; P < 0.001) and no postoperative radiation therapy (HR 39.1; 95% CI 15.5–99.6; P < 0.001), while it was negatively associated with age (HR for unit increase 0.98; 95% CI 0.97–0.99; P < 0.01) and presentation as asymptomatic incidentalomas (HR 0.30; 95% CI 0.12–0.74; P < 0.01). Other characteristics, such as sex and preoperative extension into the cavernous sinus, were not associated with the risk of tumor recurrence. We next repeated the same
analysis in the subgroup of patients without postoperative remnants as a way to reduce the strong effect of postoperative radiotherapy. Again, the risk of tumor recurrence was negatively associated with age (HR for unit increase 0.98; 95% CI 0.96–0.99; P < 0.01) and presentation as asymptomatic incidentalomas (HR 0.20; 95% CI 0.06–0.64; P < 0.01). Reclassification of the 11 postmenopausal women with gonadotropin deficiency from the asymptomatic to the symptomatic group did not significantly change the results.

**Discussion**

Incidentally discovered NFPAAs are increasingly recognized and there is general agreement that microincidentalomas should not be treated but subjected to neuroradiological monitoring, while the ongoing therapeutic debate involves endocrine inactive macroincidentalomas only (15). However, there are no robust data on surgical treatment of incidentalomas to base sound therapeutic recommendations. Our study is the largest series of incidentally discovered NFPA treated by surgery. Despite the retrospective nature of the study, the data were recorded prospectively according to a definite protocol (2). To permit a comparison with other studies, the definition of incidentalomas strictly adheres to that in the literature (15, 22). Reclassification of the 11 postmenopausal women with gonadotropin deficiency from the asymptomatic to the symptomatic group did not significantly change the results.

The prevalence of incidentally discovered NFPA ranged between 9 and 21% in other similar surgical series (23, 24, 25). The reasons to perform the initial neuroradiological examinations in our patients were similar to those described by other authors (3, 4, 7, 8, 9, 10).

Previous studies on incidentally discovered NFPA reported a male preponderance ranging from 52 to 75% (3, 8, 10). Our data confirm a gender imbalance. However, this was entirely due to the high frequency of male patients with symptomatic incidentalomas (80%). The likely explanation for this difference is the higher prevalence of hypogonadotropic hypogonadism in males than in females (46.6 vs 29.9% respectively), since the diagnosis of hypogonadism is often overlooked in aging males. Moreover, classification of postmenopausal women with inappropriately low or normal gonadotropin levels in the asymptomatic group may have contributed to increase this unbalanced gender division.

Clinical characteristics of patients with incidentalomas suggested a less aggressive NFPA than patients...
whose tumor was not incidentally discovered. However, except for age, the favorable characteristics were almost completely accounted for by asymptomatic incidentalomas, supporting the concept that distinction based on actual symptoms rather than on the way the tumor was discovered might have more therapeutic and prognostic importance.

Surgical removal of the pituitary tumor was very safe in patients with incidentalomas: no perioperative deaths were recorded and the incidence of major and minor complications was minimal. In particular, the risk of new onset hypogonadism, hypothyroidism, hypoadrenalism, and diabetes insipidus in asymptomatic incidentaloma was 5.2, 2.7, 5.3, and 6.8% respectively.

Radical removal of the tumor occurred more frequently in patients with asymptomatic incidentalomas than in either patients with symptomatic incidentalomas or the control group. This result comes as no surprise when we consider the higher frequency of favorable clinical characteristics in patients with asymptomatic incidentalomas than those in the other two groups, as delineated above. However, multivariate analysis confirmed that the better outcome in asymptomatic patients was not confounded by all the other clinical characteristics. The independent prognostic factor of incidentalomas has never been previously reported. In a previous paper (2), we also failed to find an independent favorable effect of being diagnosed as incidentaloma on surgical outcome. The likely explanation of these contrasting results lies in the larger sample of the present series and the failure to distinguish between symptomatic and asymptomatic incidentalomas in previous studies.

Recurrence of NFP A after surgery is reported between 12 and 45% (2, 23, 26, 27, 28). This variability reflects different surgical expertise, different criteria to define recurrence, the length of follow-up, and the use of postoperative radiotherapy (28). Incomplete removal is strongly associated with recurrence of NFP A (2, 23, 27, 29, 30), while adjuvant radiotherapy is very effective in reducing the risk of tumor regrowth (2, 30, 31). Our results show that patients with asymptomatic NFP A have a lower risk of tumor recurrence (HR of 0.30) than that of patients with symptomatic NFP A that is independent of all other characteristics, including the presence of postoperative remnants and utilization of radiotherapy. We are not aware of similar findings in the literature. Again, the very large sample size of the present series increased the statistical power of the study and allowed us to catch the different long-term outcome between asymptomatic incidentalomas and symptomatic tumors.

Our study has several potential drawbacks, as is unavoidable in a surgical series spanning almost 20 years. We cannot know whether external referral of patients with incidentalomas to our center has changed over the years and how many other patients with pituitary incidentalomas have not been referred to us. It is highly likely that the referral pathway to our neurosurgical center may select patients with a strong personal preference for surgical treatment of the pituitary lesion. However, our internal policy has been constant over time, as we have always thoroughly discussed with the patients the pros and cons of surgery in this setting. We have always discouraged patients with small lesions (below 1 cm) to perform surgery, unless it is a clearly demonstrated tumor growth. The balance between patient’s age and tumor size was always considered to inform the patient about the risks of surgery and, on the other side, the probability to develop clinical symptoms in the future. Diagnostic workup and surgical technique (20) has not changed at our center during the period of the study, as confirmed by the lack of a significant effect of the year of surgery on the probability of complete tumor removal. We did not consider GH function to classify patients into symptomatic and asymptomatic groups because we could perform a formal test of GH secretion in only 40% of our patients. Definition of adrenal function in this study is different from that usually suggested. However, the long study period and logistic restraints forced us to simplify classification of adrenal function by considering morning basal cortisol level and clinical response to glucocorticoid replacement in doubtful cases rather than the response to stimulation tests. Other authors reported that morning basal cortisol level using a cutoff of 80 ng/ml was well correlated to the low-dose ACTH test response in patients undergoing surgery for NFP A (32). Even though misclassification of adrenal function...
may have occurred in some cases, we think it is unlikely to affect our main results.

What is the impact of our results on actual clinical practice? Should patients with asymptomatic NFPA be advised to undergo regular monitoring of the lesion or be offered surgery? Our study does not provide a direct answer to the question, as we did not have a randomized group of patients with asymptomatic NFPA not subjected to surgery. On the other hand, a prospective randomized controlled trial of sufficient sample size on this topic is almost impossible to implement in the near future. However, by reviewing the literature on the natural history of untreated symptomatic NFPA and incidentally discovered NFPA, the rate of tumor growth during the follow-up period ranged from 7 to 50% (3, 4, 5, 6, 8, 9, 19, 33, 34, 35). Furthermore, in their meta-analysis Fernández-Balsells et al. (17) estimated that during the follow-up the tendency of tumor growth was 12.5% per year (95% CI 7.9–17.2%), the risk of new endocrine dysfunction was 2.4% per year (95% CI 0.0–6.4%), and the risk of worsening of the visual field was 0.65% per year (95% CI 0.47–0.82%). Therefore, our results can reassure patients who choose surgical removal of asymptomatic and incidentally discovered NFPA that early and late outcome is very good at the expense of minimal risks of the surgical procedure, including a low risk of developing new pituitary deficiencies.

In conclusion, our study shows for the first time in a multivariate analysis that patients with asymptomatic NFPA after surgery have a better early and long-term outcome than patients with symptomatic NFPA and an acceptable rate of serious and minor complications. The improved outcome is independent from all the other demographical, clinical, and morphological characteristics of the patients, including tumor size and invasiveness into the cavernous sinus. In our surgical series, the distinction between symptomatic and asymptomatic tumors may be more relevant for the early and long-term prognosis of the patients than the standard classification into incidentalomas or not.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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