Congress of Neurological Surgeons

GUIDELINES

CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON POSTTREATMENT FOLLOW-UP EVALUATION OF PATIENTS WITH NONFUNCTIONING PITUITARY ADENOMAS

Sponsored by

Congress of Neurological Surgeons (CNS) and the AANS/CNS Tumor Section

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Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)

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CT: Computer tomography; MRI: Magnetic Resonance Imaging; NFPA: Nonfunctioning Pituitary Adenoma; FPA: Functional or Secretory Pituitary Adenoma; RT: Radiation Therapy; FSRT: Fractionated Stereotactic Radiation Therapy

ABSTRACT

Background: Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors. Due to the lack of hormonal hypersecretion, posttreatment follow-up evaluation of NFPAs is challenging.

Objective: To create evidence-based guidelines in an attempt to formulate guidance for posttreatment follow-up in a consistent, rigorous, and cost-effective way.

Methods: An extensive literature search was performed. Only clinical articles describing postoperative follow-up of adult patients with NFPAs were included. To ascertain the class of evidence for the posttreatment follow-ups, the authors used the Clinical Assessment evidence-based classification.

Results: Twenty-three studies met the inclusion criteria with respect to answering the questions on the posttreatment radiologic, endocrinologic, and ophthalmologic follow-up. Through this search, the authors formulated evidence-based guidelines for radiologic, endocrinologic, and ophthalmologic follow-up after surgical and/or radiation treatment.

Conclusion: Long-term radiologic, endocrinologic, and ophthalmologic surveillance monitoring after surgical and/or radiation therapy treatment of NFPAs to evaluate for tumor recurrence or regrowth, as well as pituitary and visual status is recommended. There is insufficient evidence to make a recommendation on the length of time of surveillance and its frequency. It is recommended that the first radiologic study to evaluate the extent of resection of the NFPA be performed 3 or more months after surgical intervention.

RECOMMENDATIONS

Question

What is the optimal protocol for posttreatment imaging of nonfunctioning pituitary adenoma (NFPA) patients?

Target Population

These recommendations apply to adult patients with recurrent or residual NFPAs.

Level III Recommendations

- The use of MRI with the addition of T2 and T1 Weighted Images with fat suppression sequences is recommended for radiologic follow-up of NFPAs after surgical or radiation treatment.
- Long-term radiologic surveillance monitoring after surgical or radiation therapy treatment of NFPAs to evaluate for tumor recurrence or regrowth is recommended. There is insufficient evidence to make a recommendation on the length of time of surveillance.

- It is recommended that patients who undergo radiologically proven gross total resection of the NFPA be followed less frequently than those undergoing subtotal resection.
- It is recommended that the first radiologic study to evaluate the extent of resection of the NFPA be performed 3-4 months after surgical intervention.

Level Inconclusive Recommendations

- There is insufficient evidence to make a recommendation regarding the frequency of radiologic surveillance follow-up after surgical or radiation treatment of patients with NFPAs.
- There is insufficient evidence to make a recommendation regarding the timing of initial radiologic follow-up after radiation therapy.

Question

What is the optimal protocol for posttreatment endocrine evaluation of NFPA patients?

Target Population

These recommendations apply to adult patients with recurrent or residual NFPAs.

Level III Recommendations

- Endocrine evaluation for pituitary dysfunction is recommended after surgery and/or radiation therapy in patients with NFPAs.
- Postoperative evaluation of adrenal function on postoperative day 2, 6 weeks, and then 12 months after treatment is recommended to determine adrenal function in patients with NFPAs.
- Corticosteroid supplementation in the perioperative period is recommended for NFPA patients with preoperative or immediate postoperative (day 2) hypocortisolemia.
- Postoperative endocrinologic follow-up in patients with normal pituitary function beyond 1 year is not recommended, as it does not offer any further benefit.
- Indefinite endocrinologic follow-up is recommended in all patients with abnormal pituitary function who undergo surgical resection of NFPAs.
- Indefinite endocrine follow-up is recommended in patients who undergo radiation therapy for NFPAs for serial surveillance of their pituitary function.
- Surveillance of serum sodium levels on the first 2 days after surgery and on postoperative days 7-8 is recommended to prevent symptomatic postoperative hyponatremia.

Level Inconclusive Recommendations

- There is insufficient evidence to make a recommendation on the detection and treatment of postoperative diabetes insipidus (DI).
- There is insufficient evidence to make a recommendation regarding the frequency of endocrinologic follow-up evaluation after surgery or radiation therapy.

Question

What is the optimal protocol for posttreatment ophthalmologic evaluation in NFPA patients?

Target Population

These recommendations apply to adult patients with recurrent or residual NFPAs.

Level III Recommendation

Postoperative ophthalmologic follow-up in patients undergoing surgical and/or radiation therapy treatment for NFPAs is recommended to evaluate the change in visual field and visual acuity postoperatively. There is insufficient evidence to make a recommendation on the length of time for this surveillance and the frequency.

Question

What is the role for combined posttreatment follow-up (integrated imaging, ophthalmologic, and endocrine evaluation) in NFPA patients?

Target Population

These recommendations apply to adult patients with recurrent or residual nonfunctioning pituitary adenomas (NFPAs).

Level Inconclusive Recommendation

There is insufficient evidence to make a recommendation on how to integrate radiologic, ophthalmologic, and endocrinologic follow-up after surgical resection or radiation treatment of patients with NFPAs.

INTRODUCTION

Rationale

Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors.[1] Treatment options include observation, surgical resection, and/or radiation therapy. Due to the lack of hormonal hypersecretion, their initial diagnosis and postoperative follow-up evaluation is challenging. Indeed, the extent of surgical resection of NFPAs can be difficult to assess and depends on surgeon's impression, improvement of clinical symptoms, and postoperative imaging.[2] Furthermore, interventions designed to treat these lesions are poised to cause anatomical and functional changes of the pituitary gland and other sellar and parasellar structures that need to be detected and treated as necessary. These changes are assessed by clinical examination (eg, ophthalmologic examination), measurements of serum electrolytes and hormonal levels, and imaging studies. In addition, hormonal and electrolyte alterations as well as residual tumor size need to be followed for years after first treatment.[3] Currently, there is a lack

of evidence-based guidance regarding the type, frequency, and duration of radiologic, endocrinologic, and ophthalmologic follow-up.

A dearth of literature specifically addresses follow-up after treatment of NFPAs. The majority of the studies have described a blend of NFPAs and secreting/functioning pituitary adenomas (FPAs), despite surveillance differing between these tumor types. Other studies have reported results in mixed-age populations. In addition, while several authors have described the long-term posttreatment follow-up on patients undergoing surgical and/or radiation therapy treatment, few studies specifically address how to perform the follow-up, what parameters to use, and the difference in outcome with different types of follow-up schedules and hormonal evaluation.

Given this lack of evidence-based guidance and the necessity for long-term follow-up in a consistent, rigorous, and cost-effective way, a comprehensive search and evaluation of the available and relevant literature on this topic was carried out in an attempt to formulate guidance for posttreatment follow-up of these tumors and to identify areas that require additional studies. Guidelines were designed to address issues such as the need for radiologic, endocrinologic, and ophthalmologic posttreatment follow-up, the frequency of which these specific surveillance modalities should be performed, and the length of time. Furthermore, we sought to address the question whether there is a need for corticosteroid administration to these patients and the frequency of monitoring for any electrolyte imbalance.

METHODOLOGY

Process Overview

The evidence-based clinical practice guideline task force members and the Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) conducted a systematic review of the literature relevant to the management of NFPAs. To develop the evidence-based guidelines for posttreatment follow-up in patients with NFPAs, the selected articles were ranked by the relevance of the study design. In order to generate the appropriate recommendations, the studies that fulfilled our inclusion criteria were evaluated objectively, and their strength of evidence was classified using Patient Assessment criteria. The studies in which the intraobserver and interobserver agreement was reported were classified as Class I if the index of concordance κ was 0.60 or greater, as Class II if the κ was 0.40 or greater, and as Class III if the κ was less than 0.40 or not reported at all. Additional details of the systematic review are provided below and within the introduction and methodology chapter of the guideline.

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. This guideline is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in its development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical

advice or assistance is required, the services of a physician should be sought. The recommendations contained in this guideline may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Potential Conflicts of Interest

All NFPA Guideline Task Force members were required to disclose all potential COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee (JGC). The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs.

Literature Search

After an extensive search on PubMed and the Cochrane Central Register of Controlled Trials databases, 579 articles were located (see Figure 1). The duplicates from the search in different databases were eliminated. By reviewing the titles and/or abstracts, we excluded all articles referring to functioning pituitary adenomas and/or other sellar and parasellar pathologies and those discussing exclusively evaluation, treatment, and follow-up in patients younger than 18 years of age. We excluded as well those publications that discussed exclusively treatment options and outcomes and those discussing diagnostic methodologies before the beginning of any type of treatment. Additionally, we excluded all articles discussing experimental therapy in animal tumor models. The remaining 114 articles underwent full text review. Only 23 articles met all of the inclusion criteria and were used in formulating these evidence-based clinical guidelines. The majority of the remaining 114 articles that underwent full review were excluded because they reported only postoperative outcomes or reported long-term follow-up methods in all types of pituitary tumors with results that were not separable between NFPAs and FPAs, and the remainder because they lacked significance for our topic.

RESULTS

Imaging Evaluation

Seventeen studies met our inclusion criteria on answering our questions on the posttreatment radiologic follow-up (Table 1). Several of these studies were retrospective in nature, and few were prospective non-randomized case-controlled studies. According to the patient assessment criteria used, none of the studies reported intraobserver and/or interobserver concordance index for the conclusions reached. Hence, they were all classified as Class III evidence.

Which imaging modality/modalities are best to evaluate residual and recurrent NFPAs after treatment?

Regarding the type of imaging needed for follow-up, no study satisfied the inclusion criteria. Nevertheless, all the articles published in the post-magnetic resonance imaging (MRI) era have almost completely abandoned computed tomography (CT) and report the use of the MRI of the pituitary gland as the radiologic study of choice.

Moreover, there is only 1 study that defines the best MRI sequences to be used in the follow-up period after treatment of NFPAs.[2] Kremer and colleagues[2] prospectively followed 50 patients with NFPAs after resection with MRI performed at 3 days, 3 months, and at least 1 year after the surgery. They found that fat suppression technique applied on T1- and T2-weighted sequences was useful to distinguish postoperative hemorrhage, fat graft into the sella, and the posterior lobe of the pituitary gland.

Is there a need to perform surveillance imaging studies in patients with NFPAs after surgical or radiation therapy (RT) treatment, and for how long?

The majority of the studies that met the inclusion criteria supported continued long-term postoperative imaging surveillance. Chen and colleagues[4] prospectively followed 385 patients who underwent surgical treatment of NFPAs for a mean of 5.5 years. Postoperative MRIs were performed at 4 months after surgery and then yearly thereafter. Residual tumor was detected in 20.5% of patients. These patients were re-operated if the residual tumor was compressing the optic chiasm, and the rest were treated with radiation therapy (RT) or observation, per patients' preference. Progressive growth of residual tumor was seen in 75% of the cases. In 8.3% of the patients, the tumor recurred. They recommended long-term follow-up with different time intervals, depending on the clinical scenario. As in many of the studies discussed below, these authors did not study specifically differentiate follow-up schedules and did not study for how long the imaging follow-up surveillance should last. Soto-Ares et al[5] prospectively followed 51 patients with NFPAs who underwent transsphenoidal resection. The mean follow-up was 67 months. Thirty-four of these patients were noticed to have residual tumor on the first postoperative MRI that was performed 3-12 months after surgical intervention. In 13 of these patients, growth of the residual tumor was noted with a mean latency of 27 months. Seventeen patients that had radiologic confirmation of complete resection did not experience recurrence. Of interest in this study is that in 25 cases, the neurosurgeon thought that complete surgical resection had been achieved. But in 10 of these patients (40%), postoperative MRI showed residual tumor, and in at least 2 of them the tumor regrew during the follow-up period. The authors recommended yearly MRI follow-up for patients with residual tumor and a schedule of 1, 3, 5, and 10 years follow-up for patients with confirmed complete resection of the tumor with postoperative MRI. Again, these authors recommend this follow-up schedule based on their clinical judgment and experience, because they did not perform a rigorous study of different follow-up schedules. Lillehei and colleagues[6] reached a similar conclusion; they followed 45 patients who underwent transsphenoidal resection of NFPAs, of whom 32 patients with complete resection did not undergo RT. They were followed for a mean of 5.5 years. Two (6%) patients with confirmed gross total resection developed recurrence at 18 and 24 months, respectively, and underwent RT at the time of the recurrence, and 1 required additional surgery. Postoperative follow-up was recommended for at least 5 years. According to the results of this

study, even patients that undergo gross total resection of the tumor need to undergo long-term follow-up, because the tumor may recur in at least 2% of these patients.

In a retrospective review of a prospectively followed-up cohort of 122 patients, Greenman and colleagues[7] reported that in 41 of 78 patients with residual NFPAs on postoperative period, tumor enlargement was noticed to start at a mean time of 27.3 months (+/- 14 months). Tumor recurrence occurred in 6 of 30 patients who underwent complete initial resection with a mean time to detection of relapse of 61 months (+/- 24 months). Residual-free survival at 5 years was 80% in cases of complete resection and 30% in patients with partial resection. They concluded that patients with residual tumor are at high risk for tumor regrowth.

Reddy et al[8] retrospectively reviewed the long-term follow-up radiographic images and the tumor recurrence rate in 144 patients who underwent surgical resection of NFPAs. Observation with imaging studies ranged from 1-25.8 years (mean 6.1 years and median 4.3 years). The protocol consisted of scanning patients every year for the first 5 years and every 2 years after that. Overall recurrence was documented in 54 (34.8%) cases, and 11 (20.4%) of these showed recurrences 10 or more years after the initial surgery. The re-growth was 6.9% (2/29), 40.3% (27/67) and 45.8% (22/48) in those who had no residual tumor, intrasellar remnant only, and extrasellar remnant on their postoperative radiologic imaging, respectively. They reported a relapse rate of 67.9% at 15 years. Fifty percent of the recurrences were detected in 7 years and 95% in 17 years. No patient relapsed in the first 5 years in the group that had no postoperative residual tumor. By 5 years, tumor recurred in 41.3% of the patients with intrasellar remnant compared with 81.8% in those with an extrasellar residual tumor postoperatively. This is another study that suggests that long-term follow up, for at least 15 years, is necessary even in patients that have undergone total resection of the tumor, although they can be followed less frequently.

Pal et al[9] retrospectively studied 32 adult patients with NFPAs presenting with pituitary apoplexy and undergoing surgical intervention. Five patients with large postoperative residual tumor underwent fractionated stereotactic radiation therapy (FSRT). There was no recurrence noted in these 5 patients; in 3 of the 14 patients in whom only partial resection was achieved and who did not undergo RT, recurrence was noted at 12, 51, and 86 months after surgery, respectively. Recurrence rate was 4.3% and 13% at 2 and 5 years post-surgery. They recommended continuous imaging surveillance in patients who have undergone partial resection of NFPAs. Van den Bergh et al[10] retrospectively studied 122 patients who underwent surgical intervention for resection of NFPAs. Seventy-six patients with residual tumor had immediate postoperative RT (group 1), 28 with residual tumor were followed expectantly for growth (group 2), and 18 patients did not have any residual tumor (group 3). Ten-year local control rates were 95% for group 1 and 22% for group 2. In the second group, progression developed at a median interval of 30 months (11-95 months). They concluded that due to the wide interval ranges in which the tumors recurred, continued radiographic surveillance is mandatory for all patients with NFPAs after treatment. In addition, they discovered that one of the patients that had undergone RT post-surgery developed a meningioma 14 years later into the field of radiation. They suggested that the radiographic follow up should be performed as well to evaluate the development of secondary tumors. Unfortunately, they did not study and, as such, are not able to recommend a follow-up schedule algorithm for patients in the 3 different groups. Nevertheless, since the tumor recurred in all 3 groups, a long-term radiologic follow-up is recommended in all patients. Dekkers and colleagues[11] performed a retrospective study in 109 consecutive patients who underwent surgical resection of NFPAs with mean follow-up of 6.6

years. In 6 patients who underwent postoperative RT, no tumor regrowth was seen during the reported follow-up period. For the total cohort, the tumor-growth-free survival rates at 5 and 10 years after initial surgery were 94% and 81%. In patients with residual tumor on MRI, regrowth-free survival rates at 5 and 10 years after surgical treatment were 92% and 74%, respectively. In the patients without residual tumor, recurrence-free survival at 10 years was 100%. This study, although, not specifically studying follow-up schedules for these patients, supports the concept of the need for long-term follow-up and possibly with different follow-up schedules between patients with residual tumor as compared to those who had no postoperative residual. Ferrante and colleagues[12] reported a retrospective review of 226 patients treated in 7 centers. Treatment consisted of surgical resection with or without RT. Tumor regrowth and recurrence was investigated in 226 patients with minimum follow-up of 5 years. Seventy-three patients did not show radiographic evidence of residual tumor post-surgery (Group A); 77 showed evidence of residual tumor, but did not undergo RT (Group B); and 76 patients with residual disease underwent RT treatment (group C). Tumor recurrence and regrowth was noticed in 19.2% of patients in group A with a mean of 7.5 years posttreatment, in 58.4% in group B with a mean of 5.3 years, and in 18.4% in group C with a mean of 8.1 years. Tumor regrowth occurred in all patients; hence, they concluded that it is necessary to follow up with imaging studies after treatment all patients with NFPAs. Colao and colleagues[3] reported a retrospective study of 84 patients with NFPAs. All 84 patients underwent surgical resection, and 72 patients with residual tumors were considered for RT, but 13 patients refused. Eighty-four patients were followed up for 1 year, 63 patients for 2-5 years, 32 patients for 6-10 years, and only 16 patients were followed up for more than 10 years. Imaging was performed preoperatively, then 3, 6, and 12 months postoperatively, then yearly after that. Tumor regrowth was noticed in 9 patients; 5 (13.5%) after 2-5 years follow-up, 2 patients after 6-10 years follow-up, and 2 after more than 10 years follow-up. In line with other authors, they suggested that long-term follow-up should be carried out in patients with NFPAs who had undergone surgery despite the use of postoperative RT or presence of residual tumor postoperatively.

Kopp et al[13] retrospectively screened and prospectively followed 16 adult patients with NFPAs who had undergone at least 1 surgical intervention. Eight patients with recurrent tumor and 8 with postoperative residual tumor underwent FSRT. Mean follow-up was 63 months (28-100 months) with 3D 1.5 Tesla MRI. Earliest size reduction of the tumor was noticed at 28 months post-FSRT. Size reduction was 26% at 36 months, 47% at 36-72 months, and 62% after 72 months, describing an inverse correlation between tumor size reduction and time from FSRT. No progressive disease was noticed in these 16 patients. The authors noticed that volumetric 3D measurements gave a better view of size reduction of the tumors than 2D measurements. Again, these authors did not specifically study a follow-up schedule algorithm for patients undergoing RT, but their results suggest that to evaluate the shrinkage of tumor after radiation, radiologic imaging should not be performed too early after treatment. In contrast, Iwata et al[14] reported a retrospective study of 100 patients with primary, recurrent, or residual NFPAs who were treated with FSRT Cyberknife (3-5 fractions). Median follow-up was 33 months. They reported a local control rate of approximately 98% at 3 years with in-field failure in 3 patients that occurred at 10, 16, and 80 months posttreatment. They recommended that, due to the distant in-field failures in 3% of patients, continued surveillance MRIs is mandatory.

Unfortunately, in the last 2 studies described, as well in the others in which some patients underwent postoperative RT, specific reasons why some patients underwent postoperative RT and some did not are not always thoroughly reported. The descriptive and observational nature

of most of the literature makes it difficult to understand how the long-term surveillance with imaging studies would change treatment management of the patients, notwithstanding the substantial costs that long-term imaging incurs. In this regard, Coulter and colleagues[15] performed a retrospective analysis of 41 patients with NFPAs. Only 33 of these patients underwent surgical resection, and 30 received postoperative RT. Median time of first postoperative MRI was 9 months, and subsequent MRIs were performed biannually or annually. Patients were not scanned anymore after residual tumor was stable in 3 subsequent imaging studies, defined as "state of no change." Four patients showed evidence of tumor regrowth post-surgery. "State of no change" was reached at 6 months at the earliest and at 120 months at the latest. Tumor growth was noted at 4 months at the earliest and at 27 months at the latest. Fifty percent of tumors reached the "state of no change" status at 30 months and 90% at 88 months. The authors concluded that radiologic follow-up beyond 3-3.5 years may not be cost-effective. Observing the tumor over the first 36 months following surgery can provide sufficient evidence regarding its propensity and rate of growth and, as such, the need for intervention or for further follow-up. They continued to suggest that further radiologic surveillance can be discontinued after the tumor has reached a steady state, and patients can be followed with regular ophthalmologic exam and endocrinologic assessment, since the decision for further treatment in their patients was dependent on the presence of symptoms and not on the mere radiologic evidence of tumor regrowth. Only 1 of the 4 patients underwent surgical debulking after recurrence. This patient showed evidence of regrowth at 9 months and visual deficits at 7 years. Unfortunately, this study suffers due to the small number of patients reported. Furthermore, it is unclear how a patient would react to the decision to stop imaging surveillance and wait for symptoms such as visual impairment or hormonal insufficiency to appear, when the rate of reversal of these symptoms after the second treatment is unknown. In addition, the authors stated that radiologic follow-up beyond 3-3.5 years is not cost-effective, without performing a cost analysis on comparing radiologic examination with ophthalmologic and endocrinologic follow-up, and economic burden on the patients' emotional status after recurrence of the tumor causes symptoms.

After reviewing the above-described studies, it appears that NFPAs tend to recur after surgical treatment, whether followed by RT or not, in 0%-75% of the cases at 10-144 months posttreatment. The rate of recurrence is lower for patients with initial complete resection (0%-19.2%) at a maximum of 12-year follow-up; it is higher (up to 75%) in patients that undergo surgical resection with residual tumor and do not undergo RT; and there is a slightly higher rate of recurrence than the former and definitely lower rate than the latter for the patients that undergo surgical resection followed by RT.

In conclusion, long-term radiologic surveillance monitoring after treatment of NFPAs is recommended for all patients, but the length of time for this surveillance is not defined. Furthermore, from the above studies it appears that the risk of the recurrence is smaller in patients with gross total resection and in those that undergo postoperative RT than in those with residual tumor who do not undergo RT, and, as such, a different follow-up schedule could be proposed for these 3 groups of patients. Hence, while a less frequent radiologic posttreatment evaluation can be recommended in patients who undergo gross total resection or subtotal resection followed by RT, a specific follow-up schedule algorithm cannot be recommended. In this regard, it is important to define the amount of residual tumor post-surgery. Soto-Ares et al[5] found that the neurosurgeon's intraoperative impression of completeness of NFPA resection was not accurate in 40% of the cases. As such, postoperative imaging is mandatory to define the

amount of residual tumor. In this regard, of paramount importance is the decision of when to perform the first postoperative image to establish the extent of resection.

When should the first imaging study be performed in the postoperative or post-RT period?

Kremer and colleagues,[2] in their prospective, non-randomized study, analyzed postoperative imaging in 50 patients with NFPAs. Patients underwent MRI evaluation before surgery, at 3 days, at 3 months, and at least 1 year after surgery. At 3 days postoperatively in 32 patients, it appeared as though the mass had no change in size, except that it looked less homogenous when compared to the preoperative MRI. At 3 months, any hemorrhage had resolved and there was 50% less mass effect. At 1 year, the suprasellar mass was present in only 4 patients. The fat graft was not visible at 1 year. Interpretation of the images was difficult at 3 days but was better at 3 months due to complete resolution of immediate postoperative changes such as hemorrhage and fluid collection. At 1 year, the rate and localization of residual adenomas was unchanged as compared to the imaging 3 months postoperatively. The authors concluded that postoperative imaging of NFPAs at 3 days can be misleading, and the best time for early imaging was at 3 months. They recommended applying fat suppression techniques on T1- and T2-weighted sequences to further distinguish hemorrhage, fat, and the posterior lobe of the pituitary gland. In an earlier study, Kremer at al[16] reported a smaller group of patients: 22 adults with NFPAs. There, they reached the same conclusions that imaging evaluation of postoperative residual tumor is best when performed 3 months postoperatively and that MRI is better than the intraoperative neurosurgeon assessment. In another study, Rajaraman and Schulder[17] reviewed 14 patients, 11 of whom had NFPAs. They performed postoperative MRI studies within 1 week, at 3 months, and up to 1 year. They reported that early postoperative MRI scans revealed minimal reduction in mass effect, although the postoperative mass appeared less homogenous and lacked uniform enhancement. Late postoperative MRI showed significant reduction in size of the mass in all patients. They concluded that in view of the persistence of post-surgical changes for up to 4 months after surgery, optimal assessment of residual tumor could not be made until after that time. Berkmann et al[18] reached a similar conclusion when they reported their experience with 140 patients treated for NFPAs. At 3 months postoperatively, the residual mass appeared significantly smaller when compared to the immediate postoperative MRI.

In summary, as suggested by these studies, immediate postoperative radiographic studies may be misleading in determining the amount of tumor residual. To determine the amount of tumor residual with the intent to formulate future treatment plans, postoperative MRI should be performed at 3-4 months after surgery. Nevertheless, if there are concerns of adverse clinical changes observed in a patient who has undergone surgical resection of an NFPA, imaging studies in the immediate postoperative period are not contraindicated.

It is unclear when the immediate post-RT radiographic imaging should be performed. Kopp et al,[13] when reporting on the 16 patients with NFPAs who underwent FSRT after recurrence of the tumor (8 patients) and residual tumor (8 patients), noticed the earliest size reduction at 28 months. But Iwata et al,[14] who reported 100 patients that underwent Cyberknife radiation after surgical resection, noticed distant in-field failure at 10 months in 1 patient and at 16 months in another patient. Hence, a consideration should be given to perform the surveillance MRI after RT, with a similar schedule as that of post-surgical MRI, at 3 months and 1 year after treatment; nevertheless, no recommendations could be given on this regard.

While long-term follow up after treatment of NFPAs is recommended and the earliest MRI to evaluate the postoperative residual tumor should be performed 3-4 months post-surgery, an additional question is how frequently these patients should undergo surveillance radiologic evaluation.

At what time intervals should patients with NFPAs undergo follow-up imaging studies after surgical or radiation therapy treatment?

Chen and colleagues,[4] in their report of 385 patients with NFPAs, recommended performing the first postoperative MRI at 4 months, then 1 year postoperatively, and then yearly or with alternated intervals, depending on the clinical scenario afterwards. Greenman and colleagues[7] followed their 122 patients with surveillance MRIs at 3, 6, and 12 months after surgery, yearly thereafter for 5 years, and every 2 years thereafter. Patients who had received complete resection had low risk for recurrence (6 out of 30 patients with mean time to detection of relapse at 61 months); patients with residual disease were at higher risk (41 out of 78 patients with a mean time for tumor regrowth at 27.3 months). They suggested that shorter follow-up time intervals are required for high-risk patients. Soto-Ares et al[5] gave the same suggestion, although they were more specific in the time intervals. According to the authors, MRIs should be performed at 4, 12, and 24 months postoperatively. Then, in cases of complete resection, the MRI may be performed at 3, 5, and 10 years after surgery. For cases in which tumor residual exists, yearly MRIs were suggested. Nevertheless, these authors recommended these interval follow-up times based on their experience and not based on rigorous comparison study of different schedules. In their report, Kremer at al[16] noticed that biannual evaluation for 2 years did not demonstrate any changes in residual tumor volume in 22 patients followed up prospectively, with 11 of them showing residual tumor at 3 months postoperative MRI. After reviewing 140 patients with residual tumor after surgical intervention for NFPAs, Berkman and colleagues[18] reported that there was no significant change occurring in the interval time between 3 months and 1 year. Ferrante et al[12] reported that patients without postoperative residual tumor and those who underwent adjuvant radiotherapy showed a similar risk of tumor recurrence or regrowth (19.2% and 18.4%, respectively); patients with residual tumor that did not undergo RT showed regrowth in 58% of the cases. From these data, they suggested a close follow-up with serial MRIs every 12-18 months for at least 10 years in all patients. Pal et al[9] also suggested that patients with residual tumor that do not undergo postoperative RT need closer radiographic follow-up. This is consistent with the data reported by van den Bergh et al,[10] in which the recurrence rate in patients with residual tumor who did not undergo RT was 57%, while the recurrence rate in patients who did undergo RT was only 4%. Reddy et al[8] reported that patients with residual tumor postoperatively in the extrasellar compartment had a higher risk of earlier recurrence than patients with residual tumor in the sella, while patients with gross total resection had lower risk of recurrence. They suggested that the latter patients could undergo a less frequent follow-up when compared to the former.

Although none of the above cited studies suggest any particular follow-up time interval, it appears that for the first 2 years an annual imaging surveillance should be performed for all patients, then depending on the clinical circumstances; a shorter time-interval is suggested for patients who have a residual tumor and do not undergo postoperative RT or who have tumors with concerning biological features. For patients who have no residual tumor or those with residual tumors that undergo RT, the time-interval can be longer—eg, every 2-5 years. However, these need further prospective studies. In addition, studies should focus as well on how these

follow-up time intervals influence treatment decision and patient well-being when considering their hormonal and visual symptomatology.

Endocrine Evaluation

As NFPAs lack the stigmata of the clinical hypersecretory state associated with functioning tumors, they are diagnosed either incidentally or after they have reached significant size to impinge upon the visual apparatus or pituitary gland. As such, they cause pituitary dysfunction with hyposecretion of 1 or more hormones. Surgical intervention and RT can improve pituitary secretory function, but not always. For these reasons, the endocrine function of the pituitary gland needs to be evaluated after surgery and RT in order to appropriately treat any dysfunction. To support our recommendation, studies that provide Class I data are missing. There were only 7 studies—3 prospective followed case series and 4 retrospective studies—that fulfilled our inclusion criteria and provide Class III evidence regarding the need for endocrinologic follow-up after treatment of NFPAs. According to the Clinical Assessment criteria used, none of the studies reported the intraobserver and/or interobserver concordance index for the conclusions reached. Hence, they were all classified as Class III.

Is there a need for endocrinologic follow-up of patients with NFPAs who have undergone surgical or radiation therapy treatment, and for how long?

Berkmann et al[19] retrospectively reviewed 210 patients with NFPAs. Endocrine testing was performed preoperatively, 7 days postoperatively, and 3 months postoperatively. The majority of the patients (73%) presented with some elements of hypopituitarism, and 64% had not improved their pituitary function at the last follow-up. At 10 days after surgery, 33% of the patients showed recovery of their pituitary gland function. At 12 months, another 11% of patients showed recovery of 1 or more of the pituitary axis. In total, 66% of patients experienced some degree of recovery during the entire follow-up period. The authors suggested re-testing of pituitary function months after treatment to identify those patients who have a late recovery of pituitary function and could be removed from lifelong hormone substitution therapy. Chen and colleagues[4] prospectively observed 385 patients with NFPAs and reported that the majority of the patients (60%) presented with disruption of at least 1 hormonal axis (Table 2). They reported that hormonal deficiency was common and difficult to restore, suggesting the need for long-term follow-up. From the above-mentioned studies, it is clear that endocrinologic follow-up post-surgery is needed, but clarity as to the length of follow-up is not provided. It is understandable that patients with pituitary dysfunction would need posttreatment long-term follow up for hormonal substitution therapy, but there are few indications in this regard for those patients who recover their pituitary function post-surgery.

Regarding patients who undergo RT, there are very few studies that have described the pituitary functional status after such treatment. In their article, Pollock and colleagues[20] retrospectively reviewed 62 patients with primarily and recurrent NFPAs who underwent stereotactic radiation therapy (SRT) with a median follow-up of 64 months. The 5-year risk of developing new anterior pituitary functional deficit was 18% in tumors smaller than 4 cm^3 in volume and 58% for patients with a tumor volume of larger than 4 cm^3. They concluded that patients with NFPAs who undergo SRT should undergo endocrinologic evaluation secondary to the increased risk of posttreatment pituitary hormonal dysfunction. Colao et al[3] described 84 patients with NFPAs who underwent first surgical resection. Seventy-two patients with residual tumor were referred

for post-surgical RT, but 13 refused. Endocrine function was assessed preoperatively, then 1-3 months postoperatively, then quarterly in the first year and yearly after that. Sixty-two of 84 patients presented with hypopituitarism preoperatively. Of 84 patients, 16 maintained normal pituitary function post-surgery, 8 improved, and 34 worsened. In 59 patients who received post-surgical RT, there was a notable impairment of the pituitary function that was noticed at 2.5 years post-radiation. Prevalence increased from 28.8% 1-year post-radiation to 92% after more than 10 years post-radiation. They recommended long-term endocrinologic follow-up in patients who had undergone RT. In a retrospective analysis of 33 patients with NFPAs, Tominaga et al[21] described only patients who had been followed up for more than 10 years. Fourteen patients had total resection, 12 subtotal, and 7 partial. Postoperative RT was performed in 8 patients and was started 1 month after surgery. Pituitary function was evaluated pre-surgery, then at 2 weeks, 3, 6, and 12 months post-surgery, and yearly afterwards. In 2 patients, endocrinologic evaluation was done only 1 year after the surgery. Preoperatively, 30 out of 31 patients showed growth hormone (GH) impairment, deficiency of luteinizing hormone (LH) was noticed in 16 patients, adrenocorticotrophic hormone (ACTH) in 15, follicular stimulating hormone (FSH) in 13, thyroid stimulating hormone (TSH) in 6, and prolactin in 2. Hyperprolactinemia was noticed in 13 patients. Axis restoration occurred within 3 months in 85% of patients and took up to a year in others. No patients had improvement after 1 year. In patients who underwent gross total resection, there were no hormonal dysfunctions seen postoperatively. In patients who underwent subtotal resection, some developed recurrence of hormonal dysfunction secondary to regrowth. In patients who underwent only partial resection, hormonal dysfunction re-occurred after 1 year. Patients who underwent RT developed impairment of anterior pituitary function 8-9 years after RT and 2 patients even after 11 years. The authors concluded that in patients who undergo total resection of tumor, the results of the test 1 year after surgery indicate their future pituitary function and can be exempted from future endocrinologic follow up if pituitary gland function is normalized. For all other patients, and especially for those undergoing RT, periodic long-term examination is recommended.

Based on the results of these Class III studies, we can recommend that patients with NFPAs need frequent posttreatment endocrinologic follow-up, especially during the first year. For those patients who have undergone gross total resection, the endocrinologic follow-up can be stopped after 1 year if pituitary function returns to normal. All other patients, and especially those who have undergone RT, need to be followed indefinitely with yearly assessment.

Should corticosteroids be administered routinely to patients with NFPAs pre- and postoperatively?

Unrecognized adrenocorticotrophic hormonal deficiency in the postoperative period can cause fatigue, anorexia, nausea, vomiting, hypotension, fever, metabolic changes, and rarely death.[22] In response, different institutions have implemented disparate strategies; in some centers, supplemental corticosteroids are given to all patients for several weeks before the hypothalamic-pituitary-adrenal axis function is tested, while others have advocated testing the adrenal axis after surgery and deciding on the use of corticosteroid supplementation only if a dysfunction is found. This later approach has the advantage of reducing the side effects to the patients deriving from supplemental steroids and reducing healthcare costs, yet with the risk of undertreating deficiency in some cases. There have been several studies that have tried to answer this question, but they did not focus exclusively on NFPA patients, and their results were inseparable from those of FPA. We found only 1 prospective observational follow-up study of 72 patients who underwent surgical resection of NFPAs and reported on the need of corticosteroids

administration in the perioperative period.[1] Serum cortisol levels were measured at 08:00 during the preoperative period and on postoperative day 2. Fourteen patients had preoperative hypocortisolemia, and only 1 improved postoperatively, suggesting that patients with preoperative hypocortisolemia rarely improve after the surgery and, as such, should receive supplemental corticosteroids in the perioperative period. Six out of the other 58 patients developed postoperative hypocortisolemia, implying that the majority of patients with normal cortisol levels in the preoperative period maintains their eucortisolemic status postoperatively and do not need supplemental corticosteroid administration. In all but 1 patient the normal cortisol level on postoperative day 2 was confirmed at 6 weeks and 1 year. At 1 year, the results of patients with normal stimulation test performed at 6 weeks were confirmed. The authors suggested that the level of serum cortisol on postoperative day 2 should guide the need for future prescription of postoperative steroids. They suggested as well that the perioperative corticosteroid supplementation should be reserved only for patients with preoperative hypocortisolemia, and postoperative corticosteroid supplementation should be prescribed only to those patients who are discovered to be hypocortisolemic on postoperative day 2.

In summary, with the acknowledgment that this is a single study providing class III evidence, we can recommend that perioperative corticosteroid supplementation be reserved only for NFPA patients with documented preoperative hypocortisolemia. Furthermore, from these data we can recommend that postoperative corticosteroid supplementation be continued in these later patients and instituted only in those patients who in the morning of postoperative day 2 have evidence of hypocortisolemia. Follow-up of cortisol levels after surgery is recommended at 6 weeks and 1 year, or as clinically indicated by patients' symptomatology.

How often and for how long should the patients with NFPAs be monitored for serum electrolyte imbalance?

Changes in sodium homeostasis in the postoperative period have been reported in patients with pituitary adenomas. We found only 1 study that fulfilled our inclusion criteria. Hensen et al[23] prospectively monitored postoperative urine output and sodium levels of 1571 patients with pituitary tumors, among whom 534 had NFPAs. Urine output and serum sodium were monitored for 10 days after surgery, then 3 months after surgery for 24 hours, then 1 year after surgery for another 24 hours. They defined 6 patterns, based on the time of onset of polyuria; early versus late, associated with or without hyponatremia. Of the 534 patients with NFPAs, 138 (26%) suffered immediate postoperative polyuria and 51 (10%) developed prolonged polyuria without hyponatremia. Eighteen (3%) developed early postoperative hyponatremia (Na <132 mEq/L), 17 (3%) delayed hyponatremia, 20 (4%) developed a bifasic pattern (immediate postoperative polyuria at day 1-3, followed by hyponatremia), and 8 (1%) showed a triphasic pattern (prolonged polyuria for 7 days with hyponatremic episodes). Patients were treated with fluid restriction, a salt-rich diet, and oral sodium supplementation. They concluded that disturbances in osmoregulation resulting in polyuria and perturbation of serum sodium concentration are frequent within the first 3 and 7 days, suggesting follow-up of serum sodium levels at these intervals immediately postoperatively. Furthermore, they advised against administration of large amounts of oral fluids and intravenous hypotonic fluids in the postoperative period between 4 and 9 days post-surgery. Although the authors cautioned regarding treatment of polyuria as a sign of diabetes insipidus, they do not give particular suggestions on this topic for patients with NFPAs.

In summary, there are no studies that fulfilled our inclusion criteria that describe when and how to monitor for diabetes insipidus. There is Class III evidence that suggests monitoring patients after surgical treatment of NFPAs for hyponatremia on the first 2-3 days post-surgery and then on day 7-8 after resection. Treatment options are fluid restriction, a salt-rich diet, and, on rare occasions, hypertonic saline administration.

Ophthalmologic Evaluation

As previously mentioned, NFPAs are most commonly macroadenomas and mainly present with decreased visual acuity, visual field defects, and hypopituitarism caused by mass effect of the tumor.[24] In our review, we sought to answer questions regarding ophthalmologic follow-up such as when patients treated for NFPAs should be examined posttreatment and the interval and duration of longer-term follow-up. Only 3 retrospective studies fulfilled our inclusion criteria. They were all classified as Class III. (Table 3)

Is there a need for ophthalmologic follow-up of patients with NFPAs who have undergone surgical or radiation therapy treatment, for how long, and at what frequency?

Berkmann et al[19] followed with serial ophthalmologic examination 210 patients who underwent surgical treatment for NFPAs. Ophthalmologic examination was performed preoperatively, then 7 days and 3 months post-surgery. Visual field (VF) deficit normalization was noted in 51 patients (86%) within the first month. Improvement in visual acuity (VA) was noted in all 44 patients with preoperative deficiencies, and in 30 (68%), the VA normalized. There was no improvement noted after 1 year of follow-up. In this article, the authors do not propose any type of postoperative ophthalmologic follow-up schedule in patients with NFPAs. Furthermore, they do not suggest any possible algorithm on how ophthalmologic examination can be integrated with radiologic follow-up in these patients to diagnose progression of NFPAs. Nevertheless, in this article, the authors emphasize the concept that the ophthalmologic examination should be performed for at least 1 year to evaluate and document the progression of the visual changes. The same conclusions could be extracted from the study of Colao and colleagues,[3] who performed a retrospective analysis in 84 patients with NFPAs who underwent surgical resection followed by RT. Ophthalmologic examination was performed preoperatively, then at 3, 6, and 12 months posttreatment and annually after that. Fifty-eight patients presented with visual disturbances. Postoperatively, 43 patients experienced partial improvement in VA, and 15 regained normal visual functions. From the 59 patients who underwent post-surgical RT, 9 experienced improved vision, 17 were stable, and 1 worsened. Improvement was noticed within the first 6 months post RT. The authors suggested that long-term ophthalmologic follow-up should be carried out in patients with NFPAs who undergo RT.

In their retrospective review of 43 adult patients with NFPAs, Dekkers et al[24] evaluated VF and VA improvement after surgical intervention. Ophthalmologic examination was performed before surgery, then 3 and 12 months after intervention. VF was normal in 4 patients, severely altered in 60% of patients, moderately altered in 17%, and mildly altered in 14%. At 3 months, 60% of patients experienced improvement of VF, 30% experienced normalization, and 1 patient was worse. VA improved at various degrees in all patients. At 1 year, in 56% of the patients, VA showed continued improvement. The same was noticed with VF deficiencies. The authors concluded that postoperative follow-up of patients with NFPAs should include ophthalmologic

assessment within several weeks after surgery as well as subsequent assessments after 1 and 2 years in order to estimate the final effect of surgery on visual function.

In summary, there is class III evidence to recommend ophthalmologic assessment for at least 1 year after treatment. This assessment is recommended to estimate the final effects of surgery and RT on visual function. There are no reports whatsoever that have studied the value of ophthalmologic follow-up in order to detect early worsening or new deterioration of visual function in patients who have previously undergone treatment for an NFPA to signal regrowth of the tumor. In this regard, it is useful to recall for discussion the study of Coulter et al,[15] who recommended to stop radiologic imaging after a "steady state of growth" has been reached by the tumor, and follow-up with endocrinologic and ophthalmologic evaluation should be continued in order to detect tumor recurrence. Nevertheless, these authors did not give any suggestions regarding the time interval of these assessments, and, furthermore, they did not extensively report how these evaluations correlated with tumor recurrence in the imaging studies, how these findings changed the management of the patient, and whether the patient returned to baseline after treatment.

All considered, there is Class III evidence that radiologic follow-up remains the best method to evaluate the tumor for regrowth or recurrence after surgery and RT and avoid recurrence of endocrinologic dysfunction and visual disturbances.

DISCUSSION

Future Research

In conclusion, despite the large number of studies that have evaluated the outcome of treatment of NFPAs, Class I evidence providing definitive guidelines on the follow-up timeline after treatment is lacking. Currently, acknowledging the limitation of the studies presented here, our publication should provide direction in correctly planning future clinical trials in order to answer queries with regards to the length of time for radiologic, endocrinologic, and ophthalmologic follow-up after intervention for NFPAs and the interval of time of follow-up in a safe and cost-effective way, and should provide guidance on how to integrate these types of follow-ups to be able assist us in monitoring tumor recurrence in an efficient and cost-effective way.

Conclusion

This guideline lacks class I evidence providing definitive guidelines on the follow-up after treatment of NFPAs. The authors found 23 articles to formulate recommendations regarding the radiologic, endocrinologic, and ophthalmologic follow-up after intervention for NFPAs. Future work will need to clarify greater detail and provide guidance on how to integrate these to be able assist clinicians in monitoring tumor recurrence in a safe, efficient, and cost effective way.

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FIGURES

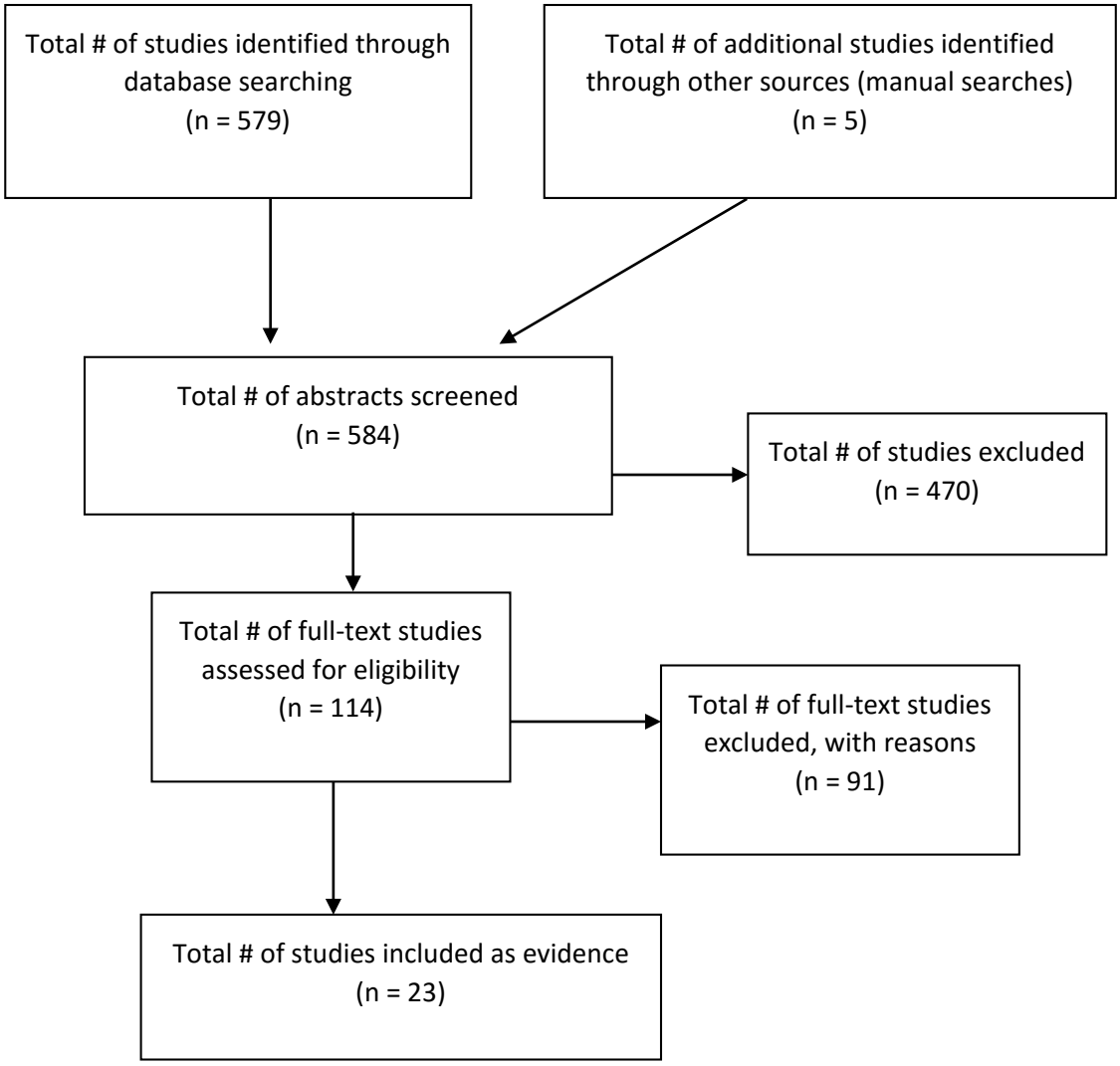

Figure 1. Article Flowchart

TABLES

Table 1: Imaging

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Kremer et al (2002)[2]	Study Design: Prospective followed case series. Patient Population: Fifty adult patients with NFPA Study Description: Patients underwent MRI before surgery, 3 days after surgery, then 3 months and at least 1 year after surgery on a 1.5T unit. Patients underwent ophthalmologic examination pre-op, immediately post op, and 3 months post-op. Patients underwent endocrinologic evaluation pre-op then 6 weeks post-op.	Clinical Assessment / III	Results: - Imaging 3 days post-op: All 32 patients with suprasellar extension of the mass preoperatively still demonstrated evidence of the presence of a suprasellar mass, but which was less homogenous. - At 3 months, hemorrhage had resolved with less mass effect by 50%, and a suprasellar mass was present in only 7 patients. - At 1 year, the suprasellar mass was present in only 4 patients. Visibility of fat graft was different and was completely absorbed at 1 year. Interpretation of images was difficult 3 days post-op, with suspected residual tumor in 25 patients. Interpretation of images was better at 3 months due to more homogenous enhancement and complete resolution of hemorrhages and post-op fluid collection, with residual tumor suspected in 15 patients. At 1 year, the rate and localization of residual adenoma tissue was unchanged as compared to the imaging 3 months post-op. Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Early post-op (3 days) MRI imaging can be misleading on the amount of residual tumor. The best time for early imaging was at 3 months. Fat suppression technique applied on T1- and T2-weighted sequences also may be useful in post-surgical MR studies to distinguish hemorrhage, fat, and the posterior lobe of the pituitary gland. Comments: Not a randomized study. The results of the diagnostic tests were reached through consensus. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Colao et al (1998)[3]	Study Design: Retrospective case series. Patient Population: Eighty-four adult patients with NFPA. Study Description: Evaluate effects of surgery followed by RT in patients with NFPA. All 84 patients underwent surgical resection; 72 patients with residual tumor were considered for RT, but 13 refused.	Clinical Assessment / III	Results: Follow-up duration was 1 year for all 84 patients, 2-5 years in 63 patients, 6-10 years in 32 patients, and 16 patients were followed for more than 10 years. - 27 patients had recurrence/regrowth of the tumor. - Tumor regrowth was noticed in 9 patients postoperatively: in 5 (13.5%) after 2-5 years follow up, in 2 patients after 6-10 years follow-up, and 2 after >10 years follow-up. - Imaging after RT: 20 patients had radiologic cure, 17 had tumor size reduction, and 11 had no change.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Imaging, CT, or MRI was performed preoperatively, then 3, 6, and 12 months postoperatively, then yearly.		Authors' Conclusions: Long-term follow-up should be carried out in all patients with NFPA who had undergone surgery or surgery followed by RT. Comments: Long-term follow-up is recommended for all patients with NFPA. A different follow-up schedule may be adopted for patients who undergo surgical treatment versus surgery and RT. Concordance index between observers for the conclusions reached was not reported.
Chen et al (2011)[4]	Study Design: Prospectively followed case series Patient Population: 385 patients with NFPA Study Description: Patients operated on for NFPA were followed prospectively for a mean of 5.5 years. Visual, imaging, and endocrinologic outcomes were noted.	Clinical Assessment / III	Results: Post-op MRIs were done at 4 months, then yearly. Residual tumor was detected in 20.5% of patients at the 4-monht MRI. Progressive growth of residual tumor remnant occurred in 75% of cases. Authors' Conclusions: NFPA should be imaged 4 months after surgery to allow postoperative changes to resolve, then 1 year after surgery and yearly thereafter or with altered intervals depending on the clinical scenario.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Comments: The authors did not compare imaging versus endocrine versus ophthalmologic outcome to define best follow-up algorithm. The authors only observed the rate of recurrence based on their follow-up schedule. They did not compare 2 different types of follow-up schedules to define the better one. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Soto-Ares et al (2002)[5]	Study Design: Prospectively followed case series. Patient Population: Fifty-one patients with NFPA undergoing transsphenoidal surgery Study Description: Patients were followed prospectively after surgery with MRIs at regular intervals to define frequency of recurrence and/or regrowth; first post-operative MRI was performed 3-12 months after surgery, 6 months later and then, every 12-18 months for at least 2 years. The mean follow-up was 67 months.	Clinical Assessment / III	Results: Thirty-four patients found to have residual tumor on the first postoperative MRI. Thirteen patients had growth of this residual tumor, with a mean latency of 27 months. It was symptomatic in 4 of these patients. Seventeen patients with complete resections had no recurrences. Authors' Conclusions: MRIs should be performed at 4-6 months after surgery and at 12 and 24 months postoperatively. MRIs may be performed at 3, 5, and 10 years after surgery in cases of complete resection. In cases in which residual tumor exists, yearly MRIs are suggested.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Comments: The authors recommend 3, 5, and 10-year interval follow-up, but they did not perform a comparative study between different schedules to define a follow-up algorithm. We can only conclude that less frequent imaging follow-up is recommended in patients with complete resection and more frequent in patients with residual tumor. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Lillehei et al (1998)[6]	Study Design: Prospective trial Patient Population: Forty-five patients with NFPA, of whom 32 had complete resection and did not undergo post-surgical RT. Study Description: Patients were followed for a mean interval of 5.5 years with radiographic imaging obtained every 6 months for the first 2 years, then annually for postoperative years 3 and 4, and then every 2 to 3 years thereafter.	Clinical Assessment / III	Results: Two of 32 (6%) patients developed recurrence, at 18 and 24 months after initial surgery. Three additional patients died as a result of unrelated causes 9, 12, and 49 months after initial surgery Authors' Conclusions: There is a 6% 5-year recurrence rate in patients with NFPA treated using gross total surgical resection (GTR) alone. Comments:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			The authors did not compare different follow-up algorithms. They describe that even patients who undergo GTR as defined by the postoperative imaging can recur, suggesting that long-term follow-up is needed even in patients who undergo GTR. The length of this follow-up is defined as at least 5 years by this study. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Greenman et al (2003)[7]	Study Design: Retrospective review of a prospectively followed patient cohort Patient Population: 122 patients undergoing surgery for NFPA Study Description: The clinical and radiographic courses of 122 patients undergoing surgery were followed for a mean of 51 months to identify predictors of recurrence and quiescence.	Clinical Assessment / III	Results: MRIs were performed 3, 6, and 12, months after transsphenoidal surgery, yearly thereafter for 5 years, and every 1-2 years afterwards or as clinically indicated. - Tumor enlargement occurred in 41 of 78 patients with residual tumor, with mean time for residual tumor enlargement = 27.3 ± 14 months - Tumor recurrence occurred in 6 of 30 patients with complete initial resections with a mean time = 61 ± 24 mo - 5-year RFS = 80% in cases of complete resection - 5-year RFS = 30% in patients with postoperative residual Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Patients with complete resections are at low risk for recurrence over the follow-up period; those with residual disease, particularly in the cavernous sinus and suprasellar region, are at higher risk for tumor regrowth. Comments: No comparison of different follow-up schedules was performed. There is not a schedule difference on frequency of follow-up in patients with GTR or STR. From the data, long-term follow-up of patients with or without postoperative residual tumor is recommended. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as Class III study.
Reddy et al (2011)[8]	Study Design: Retrospective case series Patient Population: 144 patients with NFPA who underwent surgical resection alone. Study Description: The clinical and radiographic courses of 155 patients undergoing surgery for NFPA were reviewed. Patients were followed up for 1-25.8 years (yearly for first 5 years then every 2 years).	Clinical Assessment / III	Results: Overall regrowth was seen in 54 (34%) cases; 20.4% (11/54) recurred 10 or more years after surgery. Tumor recurred in 2/29 (6.9%) patients with no residual tumor post-op, in 27/67 (40.3%) of those with intrasellar remnant, and in 22/48 (45.8%) of those with extrasellar remnant. In patients with intrasellar residual, recurrence occurred in a range of 1.3-18.3 years. In patients with extrasellar residual, recurrence occurred in a range of 1-10.8 years postoperatively.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Postoperative images were classified as: (1) no residual; (2) intrasellar residual; (3) extrasellar residual; (4) unclassified. The latter 11 patients were removed from the analysis, leaving only 144 patients.		No recurrence was seen in the first 5 years in patients with no postoperative residual tumor. By 5 years, tumors recurred in 41.3% of patients in those with intrasellar residual and in 81.8% of patients in those with extrasellar residual. Authors' Conclusions: Postoperative surveillance of NFPA needs to be continued long-term. Patients with no residual tumors after first surgery may need a less frequent imaging surveillance. Comments: No follow-up schedules are compared. This is a retrospective study. Long-term follow-up is needed to evaluate for recurrence. According to the Assessment Classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Pal et al (2011)[9]	Study Design: Retrospective case series. Patient Population: Thirty-two adult patients with NFPA presenting after pituitary apoplexy and undergoing surgical resection.	Clinical Assessment / III	Results: No recurrence was noted in 5 patients who received RT post-surgery. Three of 14 patients with partial resection had a recurrence at 12, 51, and 86 months post-surgery as detected by MRI (no symptoms).

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: Follow-up with imaging (MRI or CT) was performed preoperatively, 3 months postoperatively, yearly for 5 years, then every 2 years. Five patients underwent RT 6 months after surgery due to large residual tumor. Mean follow-up lasted 83 months (range 20-150 months). For the other 27, follow-up was for a mean of 79 months (6-248 months). Thirteen received GTR and 14 had partial resection.		Recurrence rate was 4.3% and 13% at 2 and 5 years post-surgery. Authors' Conclusions: There is an 11% recurrence rate post-surgery at just over 5 years in patients who present with pituitary apoplexy. Follow-up imaging surveillance is recommended in patients who have partial resection. Comments: No follow-up schedules are compared. The only conclusion that can be deducted is that long-term follow-up is needed for patients who undergo surgical resection of NFPA. Concordance index between observers for the conclusions reached was not reported.
Van den Bergh et al (2007)[10]	Study Design: Retrospective case series. Patient Population: 122 patients undergoing surgery for NFPA.	Clinical Assessment / III	Results: Four percent of patients in group 1 progressed compared with 57% of group 2 patients. Local control rates were 95% and 22% in groups 1 and 2, respectively, at 10 years. For group 2, progression developed with a median interval of 30 months (11-95). Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: 76 patients with residual tumor had immediate postoperative RT (group 1); 28 patients with residual tumor were followed expectantly for growth (group 2); 18 patients had no residual tumor after surgery (group 3). Patients were assessed for progression and endocrine status and followed for a median of 7.8 years (group 1) and 5.9 years (group 2).		The wide intervals in which recurrences were detected (11-95 months) mandates continued radiographic surveillance. Comments: No comparison between the 3 groups as it pertains to the radiologic follow-up schedule intervals was performed. We can recommend that long-term follow-up for patients with residual disease after surgery is needed. Concordance index between observers for the conclusions reached was not reported.
Dekkers et al (2006)[11]	Study Design: Retrospective case series. Patient Population: 109 consecutive patients operated for NFPA Study Description: This cohort of NFPAs undergoing surgery was followed for a mean of 6.0 years to determine the efficacy of a treatment strategy for NFPA that did not routinely employ postoperative RT. MRIs were performed within 6 months of surgery, 1 year after surgery, and with increasing intervals thereafter.	Clinical Assessment / III	Results: Long-term PFS was achieved in 90% of all patients. In 1 patient, recurrence occurred after 12 years follow-up. In the 6 patients treated with postoperative radiotherapy, no tumor regrowth was observed. For the total cohort, the tumor growth-free survival rates 5 and 10 years after initial surgery were 94% and 81%, respectively. In patients with residual tumor on MRI, regrowth-free survival rates 5 and 10 years after initial surgical treatment were 92% and 74%, respectively. In patients without residual tumor, recurrence-free survival rates at 5 and 10 years were 100%.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Authors' Conclusions: Patients without residual tumor have a 100% recurrence-free survival; in those with residual tumor, recurrence occurs in 26%. Comments: The authors did not specifically study the follow-up in patients with NFPA. Nevertheless, their data supports long-term follow-up in patients undergoing surgery with or without RT. A different follow-up schedule may be adopted for patients with no residual versus those with residual tumor. Concordance index between observers for the conclusions reached was not reported.
Ferrante et al (2006)[12]	Study Design: Retrospective case series. Patient Population: 295 patients from 7 centers Study Description: Imaging data were reviewed in this large cohort of NFPA patients with a mean follow-up of 5.3 years after treatment. Treatment consisted of either surgery or surgery with RT for patients with residual tumor.	Clinical Assessment / III	Results: - Seventy-three patients did not show radiological evidence of residual tumor after surgical therapy (group A). Recurrence occurred in 19.2% of patients with a mean follow-up of 7.5 years. - Seventy-seven patients showed a postoperative tumor remnant but did not undergo radiation therapy (group B). Tumor regrowth occurred in 58.4% of patients with a mean of 5.3 years. - Seventy-six patients, with evidence of tumor remnant, were treated with RT after surgery (group C). Progression occurred in 18.4% of patients, with a mean of 8.1 years.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			- Tumor regrowth of group B patients peaked after an interval of 5 years; recurrence of group A patients peaked after a 5-10 year interval; and tumor enlargement after radiotherapy in group C occurred equally across the follow-up period. Authors' Conclusions: These data suggest that a close follow-up, with serial MRI every year, is necessary for at least 10 years in all patients, even if GTR is achieved or postoperative RT for residual tumor is used. Comments: Long-term radiologic follow up is recommended in all patients, even if they undergo GTR or RT. The follow-up schedule may be different for patients with GTR versus those with residual tumor. Concordance index between observers for the conclusions reached was not reported.
Kopp et al (2012)[13]	Study Design: Retrospectively screened and prospectively followed series of patients. Patient Population: Sixteen adult patients with NFPA.	Clinical Assessment / III	Results: There was an inverse correlation between time from FSRT and relative tumor size reduction. Earliest size reduction was noticed at 28 months post-FSRT. Size reduction was by 26% (<36 months), 47% (36-72 months), and 62% (>72 months).

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: Patients had undergone at least 1 surgical intervention for NFPA. Eight with recurrent tumor and 8 with residual tumor underwent FSRT with mean radiation dose of 49.4 Gy. Mean follow-up was 63 months (28-100 months). Follow-up with 3D 1.5T MRI was every 6 months for 2 years and yearly afterwards.		No progression of disease was seen. A size reduction was noticed in only 31% of patients when measurements were made on 2D images, as compared to 100% in volumetric measurements. Authors' Conclusions: The earliest reduction in size after FSRT was noticed at 28 months. Volumetric measurement is more accurate than measurements in 2D. Comments: This study has a small number of patients. The authors followed patients for tumor shrinkage. A less frequent radiologic follow-up may be adopted for patients undergoing FSRT. Concordance index between observers for the conclusions reached was not reported.
Iwata et al (2011)[14]	Study Design: Retrospective case series. Patient Population: One hundred patients with NFPA (primary, recurrent, or remnant).	Clinical Assessment / III	Results: Local control rate at 3 years was 98%. In-field failures in 3 patients occurred at 10, 16, and 80 months. Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: Patients treated with Cyberknife in 3-5 fractions had MRI, visual, and endocrinologic assessments at 1, 3, 6, 12, and every 6 or 12 months thereafter to assess control and toxicity; median follow-up was 33 months.		Distant in-field failures after RT in 3% of patients mandate continued surveillance MRIs. Comments: Although this article did not specifically study follow-up need for NFPA patients treated with RT after surgical resection, it suggests that long-term follow up is necessary even after RT due to risk of tumor recurrence.
Coulter et al (2009)[15]	Study Design: Retrospective case series. Patient Population: Forty-one adult patients with NFPA. Study Description: Thirty-three patients underwent surgical intervention (80.4% of patients), and 8 were observed. Thirty of 33 patients received post-op RT. Median time of first post-op scan was 9 months. Subsequent scans were annual or biannual. Patients were not scanned anymore after tumor was stable in 3 subsequent imaging studies – defined as "state of no change".	Clinical Assessment / III	Results: Five patients showed evidence of tumor growth, 1 in the non-surgery group and 4 in the surgery group. One patient showed evidence of growth at 9 months and visual deficits at 7 years. "State of no change" was reached the earliest at 6 months and the latest at 120 months. Tumor growth was noted the earliest at 4 months and the latest at 27 months. 50% of tumors reached the "no-change status" at 30 months and 90% reached the status at 88 months. Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Radiological follow-up beyond 3-3.5 years is not recommended. Routine radiologic follow-up could be discontinued after the tumor has attained a steady state, and clinical follow-up with regular ophthalmologic examination and endocrine assessment should be continued thereafter. Comments: The authors did not conduct a cost analysis to define whether radiologic follow up is more cost-efficient than ophthalmologic and endocrinologic follow up. The authors did not study the rate of recurrence and/or growth of the tumor after 3 subsequent scans showed stable residual tumor. The time interval between the 3 stable scans varies from 6 to 120 months, and the time frame between these 3 scans to define the "state of no change" has not been defined. Concordance index between observers for the conclusions reached was not reported.
Kremer et al (1996)[16]	Study Design: Prospectively followed case series of patients. Patient Population: Twenty-two adult patients with NFPA.	Clinical Assessment / III	Results: At 3 months follow-up, 11 patients (50%) were noticed to have residual tumor, and in 4 (18%), findings were equivocal for scar vs residual. Biannual evaluation for 2 years did not demonstrate any changes in residual tumor volume. Authors' Conclusions:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: Patients underwent MRI (1T) evaluation immediately pre-op and 3 months post-op. Patients with suspected residual tumor underwent MRI evaluation every 6 months for the following 2 years.		Post-op MRI at 3 months is helpful to assess the completeness of tumor resection. Comments: Patients were followed prospectively, but no comparison to other follow-up schedules was made. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Rajaraman, Schulder (1999)[17]	Study Design: Prospectively followed case series. Patient Population: Fourteen patients with pituitary adenoma (11 NFPA, 2 prolactinoma, 1 necrosis) Study Description: To study MRI appearance of sella following pituitary adenoma resection. Patients underwent early MRI within 1 week postoperatively and late MRI at 3 months and up to 1 year postoperatively.	Clinical Assessment / III	Results: Early postoperative MRI scans revealed minimal reduction in mass effect; in fact, the mass appeared larger in 2 patients. The post-op mass appeared less homogenous and lacked uniform enhancement. Late post-op MRI showed significant reduction in size of the mass in all patients. Author's Conclusions: In view of the persistence of post-surgical changes for up to 4 months after surgery, optimal assessment of residual tumor cannot be made until after that time. Additional treatment for stable patients should be delayed for at least 4 months after resection of pituitary adenoma.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Comments: Not randomized study. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Berkmann et al (2013)[18]	Study Design: Retrospective case series. Patient Population: One hundred and forty patients with NPFA who were found to have residual tumor residual postoperatively. Study Description: Patients who underwent surgical resection of NFPA performed in an intraoperative MRI with residual tumor. They were followed for a mean duration of 2.7 years to assess the growth patterns of tumor remnants, with predictors of remnant shrinkage sought.	Clinical Assessment / III	Results: At the 3-month follow-up MRI, reduction in the size of tumor remnant was seen in 70 (50%) patients. Among patients not treated with further surgery or radiotherapy, no significant volume changes occurred between the 3 months and the 1 year postoperative follow-up visits. 19% of patients with reduction in the size of residual tumor underwent further treatment. In 43 (31%) patients, tumor residuals depicted by intraoperative MR images were not depicted on postoperative MR images 3 months later. Authors' Conclusions: In some patients with NFPA undergoing transsphenoidal surgery, residual mass lesions can shrink significantly in 3 months; little change appeared to occur between 3 months and 1 year.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			Comments: Immediate postoperative MRI may be deceiving in assessing residual tumor even when performed intraoperatively. Concordance index between observers for the conclusions reached was not reported.

Table 2: Endocrine

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Cozzi et al (2009)[1]	Study Design: Prospectively followed case series. Patient Population: Seventy-two adult patients who underwent transsphenoidal resection of NFPA. Study Description: To evaluate the need for postoperative steroids in patients with NFPA. Cortisol level was measured at 08:00 before surgery and on POD#2. All other hormone levels were measured as well. Patients with pre-op hypocortisolism received steroids before surgery. If	Clinical Assessment / III	Results: Fourteen patients had pre-op hypocortisolism. One out of 14 showed improvement of the hypocortisolism postoperatively. Six out of 58 patients with normal preoperative cortisol developed post-op hypocortisolemia. In all but 1 patient, the normal cortisol level on POD#2 was confirmed at 6-week tests. At 1 year follow-up all patients with normal cortisol level on POD#2 demonstrated normal cortisol level, and the stimulation test at 1 year confirmed the results of cortisol stimulation test performed 6 weeks post-op. DI occurred in 10 patients postoperatively and was permanent in 3.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	POD#2 cortisol was normal, patients did not receive steroids. Patients were re-evaluated for glucocorticoid and other hormonal requirements at 6 weeks and then after 12 months. Those with DI were evaluated 3 months and 12 months post-op.		All these data were confirmed with LDACTH test. <u>Authors' Conclusions:</u> A simple 08:00 h evaluation of free cortisol level in pre-op and on POD#2 postop should suffice to assess HPA function. Suggest that perioperative steroid treatment should be reserved for patients with low level of pituitary cortisol. The value of free cortisol on POD#2 should guide the need for future prescription of post-op glucocorticoid replacement. <u>Comments:</u> This is a prospective follow-up study and not a comparative study. The authors did not report whether patients with postoperative hypocortisolemia ever showed improvement of this function. Furthermore, while they mention the occurrence of DI in the postoperative period, they do not give any data on the immediate and long-term evaluation of this function. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.
Colao et al (1998)[3]	<u>Study Description:</u> Retrospective analysis. <u>Patient Population:</u> 84 adult patients with NFPA.	Clinical Assessment / III	<u>Results:</u> sixty-two out of 84 presented with hypopituitarism. Sixteen patients maintained normal pituitary function immediately after surgery, 8 patients improved, and 34 worsened.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Design: Evaluate the endocrine and ophthalmologic effects of surgery followed by RT in patients with NFPA. Follow-up duration was 1 year for all 84 patients, 2-5 years in 63 patients, 6-10 years in 32 patients, and 16 patients were followed for more than 10 years. All 84 patients underwent surgical resection; 72 patients with residual tumor were considered for RT, but 13 refused. Endocrine function was assessed pre-op, then 1-3 months post-op, then quarterly in the first year and yearly after that. Ophthalmologic and radiologic follow-up was performed as well.		In 59 patients who received RT 6-12 months after surgery, notable impairment of pituitary function was noticed 2.5 years post RT. Prevalence increased from 28.8% 1 year post RT to 92% after more than 10 years after RT. Authors' Conclusions: Long-term endocrinologic follow-up should be carried out in patients with NFPA who have undergone surgery and RT. Comments: The authors do not directly address the follow-up schedule for patients with NFPA who undergo surgery and RT. Nevertheless, from the data presented, we can extrapolate that due to the high incidence of pituitary insufficiency presenting more than 10 years after treatment, long-term endocrine follow-up is needed. Concordance index between observers for the conclusions reached was not reported.
Chen et al (2011)[4]	Study Design: Prospectively followed case series. Patient Population: 385 patients with NFPA followed prospectively. Study Description: This large cohort of patients was followed prospectively in order to determine the preoperative and	Clinical Assessment / III	Results: Postoperatively, GH deficiency was present in 49.1% of patients, hypogonadism in 33.2%, and hypoprolactinemia in 14.8%. Hypocortisolism was confirmed in 84 (21.8%) patients with abnormal POD#2 08:00 serum cortisol level. They were given glucocorticoid replacement. On POD#6, low serum cortisol was detected in 122 (31.7%) patients, and they were discharged on glucocorticoid replacement.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	postoperative endocrine status of patients operated on for NFPA. Electrolytes and hormones were assessed postoperatively and at 6 weeks, and as needed thereafter.		Hypothyroidism was seen in 135 (35.1%) of patients who were given levothyroxine replacement. At 6 weeks, 87 patients had hypocortisolism and 67 had hypothyroidism. At 3, 6, and 12 months, testing revealed normalization in all except 8 patients. These patients were continued in permanent hormonal replacement. Only patients with pituitary apoplexy or cortisol deficiency received preoperative cortisol replacement. Hyponatremia was evident in 22.1% of patients and improved at discharge or within 6 weeks. 18.7% had DI postoperatively; this decreased to half by discharge and to 0.8% permanently. <u>Authors' Conclusions:</u> Postoperative endocrine deficiency was common; up to 1/3 had steroid or thyroid deficiency. Appropriate follow-up of endocrine function is important to determine the need and the length of time for hormonal replacement. <u>Comments:</u> Not a randomized study. Endocrine follow-up to determine the need for hormonal replacement is recommended from these results. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Berkmann et al (2014)[19]	Study Design: Retrospective case series. Patient Population: 210 patients with NFPA. Study Description: Patients underwent surgery for initial NFPA in iMRI suite and radiologic, endocrinologic, and visual sequelae were tracked with a mean follow-up of 5 years. Endocrine testing was performed preoperatively and 7 days and 3 months postoperatively and then yearly for at least 3 years.	Clinical Assessment / III	Results: Overall, 73% of patients had an element of hypopituitarism preoperatively; this continued in 64% of patients on last follow-up. One-third of the patients already showed recovery of pituitary function within 10 days after surgery. Fifty percent showed some degree of recovery at 3 months. At 12 months, another 11% of patients showed recovery of some pituitary axis. New pituitary deficits were found in 26% of the patients. In total, 66% of patients experienced some degree of pituitary function recovery. This did not correlate with iMRI-guided resection or GTR. Authors' Conclusions: One-third of the patients already showed recovery of pituitary function within 10 days after surgery. This recovery may continue for at least 12 months; re-testing after several months may be reasonable to avoid possible lifelong hormone substitution therapy. Comments: The authors conclude that endocrinologic function may continue to improve, but they do not define the maximal length of time needed for this recovery. Concordance index

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			between observers for the conclusions reached was not reported.
Pollock et al (2008)[20]	Study Description: Retrospective case series. Patient Population: Sixty-two patients primarily and with recurrent NFPA underwent gamma knife radiosurgery. Study Design: Radiographic and endocrinologic data were obtained in only 41 of 62 patients after GK RT, with a median follow-up of 69 +/- 32 months. Thirty-four patients were followed at 3 years, and 16 were followed for more than 6 years.	Clinical Assessment / III	Results: Imaging and endocrinologic follow-up data were typically obtained at baseline, 6-month intervals after radiosurgery for the first 2 years, and yearly thereafter. New hypopituitarism developed in 11 (27%) of the 41 patients. They were detected at a median of 12 months post RT. The actuarial risk of developing new hypopituitarism at 5 years was 32%. Five-year risk of developing new anterior pituitary deficits was 18% for patients with a tumor volume of <4.0 cm^3, compared with 58% for patients with a tumor volume >4.0 cm^3. Authors' Conclusions: A primary complication of GK is hypopituitarism, and the risk of developing new anterior pituitary deficits correlates with the size of the irradiated tumor and bears longer-term hormonal testing. Comments: The paper does not specifically address follow-up schedules for patients with NFPA after GK radiation. Nevertheless, from the data, we can extrapolate that due to the risk of pituitary dysfunction, long-term endocrinologic follow up is needed in

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			these patients. Concordance index between observers for the conclusions reached was not reported.
Tominaga et al (1995)[21]	Study Design: Retrospective analysis Patient Population: Thirty-three adult patients with NFPA. Study Description: Thirty-three patients who had >10 years follow-up after surgical treatment and RT. Thirty-three patients underwent surgical resection (14 total adenomectomy, 12 subtotal, and 7 partial). Post-op RT was performed in 8 patients. RT was started 1 month after surgery. Pituitary function was evaluated preoperatively, then at 2 weeks, 3 months, 6 months, 1 year post-op, and then annually. In patients who underwent RT post-op, it was done at 2 week post-op, then 2 months, 5 months, and 1 year post RT and then annually.	Clinical Assessment / III	Results: Pre-op evaluation showed impairment of GH in 30 patients, LH in 16, ACTH in 15, FSH in 13, TSH in 6, and PRL in 2. Hyperprolactinemia was found in 13 patients. 85% of patients whose function was restored reached this stage within the first 3 months postoperatively, but it took 3 months to 1 year for the others. There was no improvement noticed after 1 year. In patients in whom total resection was performed, there was no impairment of pituitary function seen. In patients who underwent subtotal resection, some developed recurrence of pituitary hormonal dysfunction secondary to regrowth. In patients who underwent only partial resection, impairment of pituitary function occurred after 1 year irrespective of tumor regrowth. Patients who underwent RT developed impairment of anterior pituitary function 8-9 years after RT, and 2 patients even after 11 years. Authors' Conclusions: Endocrinological follow-up schedule should be decided based on the initial treatment of NFPA:

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
			- Patients who undergo total resection of tumor can be exempted from periodic endocrinologic follow-up after 1 year if pituitary function is normalized. - Patient with non-curative surgery and especially those undergoing RT require endocrinologic examination for at least 11 years. Comments: Retrospective study. The authors did not compare different follow-up schedules to find the best algorithm for post-treatment endocrine evaluation. Furthermore, the authors did not study how different follow-up modalities and radiologic, endocrinologic, and ophthalmologic evaluation could be combined for best results. Nevertheless, due to reported occurrence of hypopituitarism after 11 years, long-term endocrine follow-up in this patient population is recommended. Concordance index between observers for the conclusions reached was not reported.
Hensen et al (1999)[23]	Study Design: Prospectively followed case series. Patient Population: 1571 adult patients with pituitary adenoma, among whom 534 had NFPA.	Clinical Assessment / III	Results: Of 534 patients with NFPA, 138 (26%) suffered immediate postoperative polyuria (pattern 1), 51 (10%) developed prolonged polyuria (pattern 2), 18 (3%) developed postoperative hyponatremia (Na <132 mmol/L) (pattern 3), 17 (3%) delayed hyponatremia (pattern 4), 20 (4%) had a biphasic pattern (pattern 5), and 8 (1%) had showed a triphasic pattern (pattern 5) of polyuria and hyponatremia. Patients were treated with fluid restriction, a salt-rich diet, and oral sodium supplementation.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
	Study Description: Urine output and serum sodium was monitored for 10 days after surgery, then 3 months after surgery for 24 hours, then 1 year post-op for 24 hours. These patterns were defined: (1) immediate polyuria—occurring day 1-3 post-op without hyponatremia; (2) prolonged polyuria—occurring day 1-7 post-op without hyponatremia; (3) immediate post-op hyponatremia with or without immediate polyuria (day 1-3); (4) isolated delayed hyponatremia without polyuria; (5) biphasic course—immediate post-op polyuria, day 1-3 followed by hyponatremia; (6) triphasic course—prolonged polyuria (>7 days) with hyponatremic episodes.		Authors' Conclusions: Patients with NFPA are at risk of developing postoperative polyuria and hyponatremia. Large amounts of fluids or IV administration of hypotonic fluids should be avoided between 4 and 9 days post-op. Comments: This is not a randomized controlled trial. According to the data reported by the authors, postoperative hyponatremia with or without polyuria can occur within the first 3 days or after 7 days, suggesting follow-up of serum sodium levels at these intervals. According to the Clinical Assessment classification criteria, this study did not report the concordance index between the observers for the conclusions reached. Hence, it was classified as a Class III study.

Table 3: Vision

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Colao et al (1998)[3]	Study Design: Retrospective case series. Patient Population: Eighty-four adult patients with NFPA. Study Description: Evaluate the endocrine and ophthalmologic effects of surgery followed by RT in patients with NFPA. Follow-up duration was 1 year for all 84 patients, 2-5 years in 63 patients, 6-10 years in 32 patients, and 16 patients were followed for more than 10 years. All 84 patients underwent surgical resection; 72 patients with residual tumor were considered for RT, but 13 refused. - Ophthalmologic exam was performed pre-op, then at 3, 6, and 12 months post-op, then yearly.	Clinical Assessment / III	Results: Fifty-eight out of 84 patients presented with visual disturbances. - Immediately post-op, 43 had partial improvement in visual disturbances and 15 regained normal vision. - In 59 patients who received RT 6-12 months post-op, 9 experienced improved vision, 17 were stable, and 1 worsened. Improvement was noticed within the first 6 months. Authors' Conclusions: Long-term ophthalmologic follow-up should be carried out in patients with NFPA who have undergone surgery and RT. Comments: Retrospective study. The authors did not compare the value of endocrine function follow-up versus ophthalmologic or radiologic follow-up after surgery and RT. Ophthalmologic follow-up is recommended to document changes in visual acuity and visual fields and reassure patients on the outcome. Concordance index between observers for the conclusions reached was not reported.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Berkmann et al (2014)[19]	Study Design: Retrospective case series. Patient Population: 210 patients with NFPA. Study Description: Patients underwent surgery for initial NFPA in iMRI suite and visual sequelae tracked with mean follow-up of 5 years. Visual examinations were performed preoperatively and 7 days and 3 months postoperatively.	Clinical Assessment / III	Results: Normalization of visual field deficit was noted in 51 (86%) patients on ophthalmological follow-up examinations within 1 month after surgery. Improvement of visual acuity (VA) was noted in all 44 patients with preoperative deficiencies. In 30 (68%) patients, VA had normalized. No further improvements were noted after 1 year. Author's Conclusions: Improvement in vision is expected in symptomatic patients with NFPA; the improvements should occur within 1 year of surgery. Comments: Although authors performed radiologic, endocrinologic, and ophthalmologic follow-up, they did not report which one was better. No ophthalmologic follow-up schedule algorithm was proposed. Nevertheless, they report that improvement in vision after surgical treatment of NFPA could happen up to 1 year after intervention. Concordance index between observers for the conclusions reached was not reported.

Author (Year)	Description of Study	Classification Process / Evidence Class	Results and Conclusions
Dekkers et al (2007)[24]	Study Design: Retrospective case series. Patient Population: Forty-three adult patients with NFPA. Study Description: VA and VF were examined before surgery and 3 and 12 months after surgery in patients with compression of chiasm.	Clinical Assessment / III	Results: Preoperatively, VF was normal in 4 patients, severely altered in 60% of patients, moderately altered in 17%, and mild in 14%. At 3 months, 60% experienced improvement of VF, 30% experienced normalization, and 1 was worse. At 1 year, 36% experienced improvement of VF, and 80% of these showed improvement of VA. In 56% of the patients, VA showed continued improvement. Authors' Conclusions: Follow-up of patients after surgical treatment for pituitary macroadenomas should include ophthalmologic assessment within several weeks after surgery as well as subsequent assessments after 1 and 2 years in order to estimate the final effect of surgery on visual function. Comments: The authors do not compare whether radiologic, endocrine, or ophthalmologic follow-up is better for tumor recurrence. Long-term ophthalmologic examination is recommended for documentation of improvement of visual disturbances and patient reassurance. Concordance index between observers for the conclusions reached was not reported.

APPENDIX A

Search Strategies

Imaging

1. (("Pituitary Neoplasms"[Majr] AND Adenoma[Mesh]) OR "Adenoma, Chromophobe"[Majr] OR "Sella Turcica"[Majr])
2. (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* OR chromophobe*[Title/Abstract]) AND (pituitary OR hypophyse* OR sellar[Title/Abstract])
3. (1 or 2) and (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)
4. 3 and ("Follow-up Studies"[Mesh] OR post-treatment OR post-therap* OR "postoperative period"[Mesh]) AND ("Tomography, X-Ray Computed"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR "dynamic contrast imaging")
5. Limit to English and Humans

Endocrine

1. (("Pituitary Neoplasms"[Majr] AND Adenoma[Mesh]) OR "Adenoma, Chromophobe"[Majr] OR "Sella Turcica"[Majr])
2. (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* OR chromophobe*[Title/Abstract]) AND (pituitary OR hypophyse* OR sellar[Title/Abstract])
3. (1 or 2) and (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)
4. 3 and ("Diagnostic techniques, endocrine"[Mesh] OR (endocrine AND (function OR functioning OR status))) AND ("Follow-up Studies"[mesh] OR post-treatment OR post-therap* OR "postoperative period"[mesh])
5. 4 or postoperative steroid AND (therapy OR replacement) AND transsphenoidal
6. Limit to English and Humans

Ophthalmologic

1. (("Pituitary Neoplasms"[Majr] AND Adenoma[Mesh]) OR "Adenoma, Chromophobe"[Majr] OR "Sella Turcica"[Majr])

2. (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* OR chromophobe*[Title/Abstract]) AND (pituitary OR hypophyse* OR sellar[Title/Abstract])
3. (1 or 2) and (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)
4. 3 and ("Visual Field Tests"[Mesh] OR "Diagnostic Techniques, Ophthalmological"[Mesh]) OR ("Vision Disorders"[Mesh] OR (visual AND (deficit* OR impairment* OR disorder*)) AND ("Follow-up Studies"[mesh] OR post-treatment OR post-therp* OR "postoperative period"[mesh])
5. Limit to English and Humans

Diabetes insipidus

1. (("Pituitary Neoplasms"[Majr] AND Adenoma[Mesh]) OR "Adenoma, Chromophobe"[Majr] OR "Sella Turcica"[Majr])
2. (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* OR chromophobe*[Title/Abstract]) AND (pituitary OR hypophyse* OR sellar[Title/Abstract])
3. (1 or 2) AND (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)
4. (hyponatremia[MeSH Terms] OR hypernatremia[MeSH Terms] OR diabetes insipidus[MeSH Terms])
5. ("hyponatremia" OR "hyponatraemia" OR "hypernatremia" OR "hypernatraemia" OR "diabetes insipidus" OR "panhypopituitarism" OR "pan-hypopituitarism")
6. (postoperative steroid) AND (therapy OR replacement)
7. 3 AND (4 OR 5 OR 6)
8. 7 AND (("Follow-up Studies"[Mesh] OR "postoperative period"[mesh]) OR post-treatment OR post-therap* OR postoperat* OR post-operat*)
9. NOT comment[pt] NOT letter[pt]
10. Limits to English, Humans, publication date to 10/01/2014

Cochrane

1. MeSH descriptor Pituitary Neoplasms
2. MeSH descriptor Adenoma
3. 1 and 2
4. ((pituitary OR hypophyse* OR sellar) NEAR/4 (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* or chromophobe*)):ti,ab,kw
5. 3 or 4 and (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)