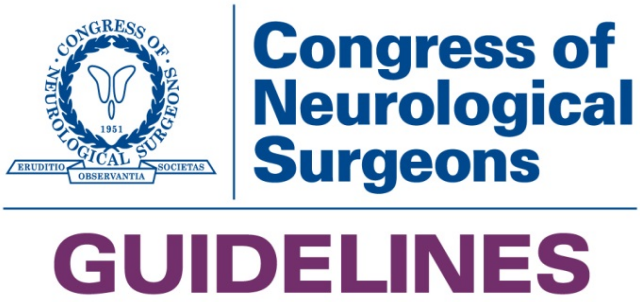

CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON SURGICAL TECHNIQUES AND TECHNOLOGIES FOR THE MANAGEMENT OF PATIENTS WITH NONFUNCTIONING PITUITARY ADENOMAS

Sponsored by

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

Endorsed by

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

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ABSTRACT

Background: Numerous technological adjuncts are used during transsphenoidal surgery for nonfunctioning pituitary adenomas (NFPAs), including endoscopy, neuronavigation, intraoperative magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) diversion, and dural closure techniques.

Objective: To generate evidence-based guidelines for the use of NFPA surgical techniques and technologies.

Methods: An extensive literature search spanning January 1, 1966, to October 1, 2014 was performed, and only articles pertaining to technological adjuncts for NFPA resection were included. The Clinical Assessment evidence-based classification was used to ascertain the class of evidence.

Results: Fifty-six studies met inclusion criteria, and evidence-based guidelines were formulated on the use of endoscopy, neuronavigation, intraoperative MRI, CSF diversion, and dural closure techniques.

Conclusion: Both endoscopic and microscopic transsphenoidal approaches are recommended for symptom relief in patients with NFPAs, with the extent of tumor resection improved by adequate bony exposure and endoscopic visualization. In select cases, combined transcranial and transsphenoidal approaches are recommended. Although intraoperative MRI can improve gross total resection, its use is associated with an increased false-positive rate and is thus not

recommended. There is insufficient evidence to recommend the use of neuronavigation, CSF diversion, intrathecal injection, or specific dural closure techniques.

RECOMMENDATIONS

Question

What is the role of technical aspects (adjuvants) of operative treatment of patients with nonfunctioning pituitary adenomas (NFPAs)?

Target Population

These recommendations apply to initial operative treatment of adult patients with NFPAs.

Question

Do transsphenoidal or endoscopic surgical approaches lead to symptomatic relief for NFPA patients?

Recommendation

Level III: Transsphenoidal microsurgery or endoscopic resection is recommended for symptomatic relief of nonfunctioning pituitary adenoma patients.

Question

What surgical approach is recommended for elderly NFPA patients?

Recommendation

Level III: The transsphenoidal approach is recommended for NFPA resection in ASA grade 1-3 elderly patients.

Question

Does bony exposure alter the extent of NFPA resection?

Recommendation

Level III: Adequate bony exposure of the sphenoid and sellar regions is recommended to improve extent of NFPA resection.

Question

Does endoscopic visualization improve visualization of NFPA tumors remaining after standard microsurgery?

Recommendation

Level III: Endoscopic approaches are recommended for better visualization of portions of tumors remaining after standard microsurgery, shown in multiple Class III studies in which direct endoscopic visualization revealed residual tumor tissue after initial microsurgery.

Question

Is a surgical strategy of combined transsphenoidal and transcranial approaches useful in NFPA surgery?

Recommendation

Level III: For select, invasive NFPAs with significant suprasellar, frontal, and/or temporal extension, the combined surgical strategy of transsphenoidal and transcranial approaches is recommended.

Question

Does use of intraoperative MRI technology improve gross total resection of NFPAs?

Recommendation

Level III: Although intraoperative MRI (low-field or high-field) helps improve immediate overall gross total resection of nonfunctioning pituitary adenomas, intraoperative MRI for estimating residual tumor is not recommended due to a reported variable false-positive rate. This false-positive rate may contribute to the higher rate of gross total resection occurring with intraoperative MRI (but at the cost of removing normal tissue) and underscores the importance of incorporating surgical experience in the interpretation of intraoperative MR imaging for surgical decision-making.

LEVEL OF EVIDENCE: INSUFFICIENT EVIDENCE

Question

Is stereotactic neuronavigation a useful adjunct for NFPA surgery?

Recommendation

There is insufficient evidence to recommend the use of neuronavigation as a useful adjunct for NFPA transsphenoidal surgery.

Question

Does introduction of intrathecal saline or air improve resection of suprasellar NFPAs?

Recommendation

There is insufficient evidence to recommend the use of intrathecal saline or air introduction for suprasellar tumor delivery to augment NFPA resection.

Question

Does perioperative CSF diversion decrease the risk of postoperative CSF leak for NFPA surgeries?

Recommendation

There is insufficient evidence to recommend the use of perioperative CSF diversion to prevent postoperative CSF leak.

Question

Is there a superior dural closure technique to prevent CSF leaks?

Recommendation

There is insufficient evidence to recommend the use of specific dural closure techniques to prevent postoperative CSF leak for NFPA resection.

INTRODUCTION

Rationale

Transsphenoidal surgery with microscopic visualization has been the standard for nonfunctioning pituitary adenoma (NFPA) resection for many decades, with technological advances in endoscopic visualization technology driving the advent of endoscopic surgical approach as a major alternative. In addition, intraoperative MRI technologies are now available at numerous sites for intraoperative imaging. This chapter surveys the literature for evidence concerning the surgical approaches of transsphenoidal microsurgery, endoscopic resection, and transcranial surgery, as well as adjunctive technological innovations such as intraoperative MRI, neuronavigation, plus technical concerns of CSF diversion and dural closure.

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. 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 Guidelines 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

The task force collaborated with a medical librarian to search for articles published from January, 1, 1966, to October 1, 2014. Authors searched 2 electronic databases, PubMed and The Cochrane Central Register of Controlled Trials. Strategies for searching electronic databases were constructed by the evidence-based clinical practice guideline taskforce members and the medical librarian using previously published search strategies to identify relevant studies (Appendix A).[1-8]

RESULTS

The medical literature was searched using search terms encompassing surgical resection strategies specific to transsphenoidal and intraoperative MRI techniques. Abstracts from the results of these searches were screened, and full-text articles from potentially significant articles were reviewed.

Articles found on literature review based on the above criteria include 35 Class III studies involving transsphenoidal microscopic surgery, 20 Class III studies for endoscopic surgery, and 9 Class III studies involving transcranial surgery for NFPA resection. A flow chart summarizing study selection can be found in Figure 1. Studies that included results from multiple or combined surgical approaches were included in several of the above categories. For this paper, transsphenoidal surgery is a broad term that includes both microscopic and endoscopic approaches. Specifically, microscopic transsphenoidal surgery or transsphenoidal microsurgery refer to surgeries performed with microscope visualization and tumor resection via either sublabial or endonasal pathways, whereas endoscopic transsphenoidal surgery refers to using endoscope visualization and resection via various anatomical corridors (usually variations of the endonasal and endosinus corridors); the transcranial approach consists of supratentorial craniotomy microscopic tumor resections.

Transsphenoidal Microsurgery

The efficacy of transsphenoidal microsurgery for NFPA resection is well documented and accepted. Twenty-four studies provide Class III evidence that transsphenoidal microsurgery is effective for removing most or all of the NFPA and improves symptoms (Table 1).[9-15]

Lillehei and colleagues showed gross total resection in 84% of patients, with only 6% recurrence after 5 years. Gross total resection was achieved in 75% of NFPA patients on early and delayed MRI assessments in Yoon's 2001 study, with only nodular residual tumor detected in the remaining 25% of patients. Kremer and colleagues reported in 2 papers that between 30%-50% of postop patients showed residual tumor at delayed (3 months and 1 year) MRI studies. With intraoperative MRI, Fahlbusch and colleagues reported successful gross total resection in 70% of NFPA patients. Regarding endocrine improvement, Arita et al reported restoring regular menstruation in 7 of 15 women (46%), with gonadotropin secretion normalized in 2 of 7 patients and prolactin level normalized in 4 of 6 patients. Flitsch et al performed a prospective study that showed postoperative improvement in emotional measures via positive changes in depression, fatigue, and excitability.

Thirteen additional studies provide Class III evidence to support the effectiveness of transsphenoidal microsurgery (Table 1).[16-28] Young et al reported on 100 NFPA surgeries (98 resected via transsphenoidal approach, 2 resected via transcranial approach), with 90% gross total resection reported, but 42% residual/recurrent tumor found after 5 or more years on follow-up CT imaging. Complications included 24% postoperative hypopituitarism and 1 death due to hemorrhage. At 73 months follow-up, Ebersold et al reported an 84% gross total NFPA resection using transsphenoidal microsurgery with intraoperative fluoroscopy in 100 patients, with 3% surgically related mortality, 1% CSF leak, and 2% need for permanent CSF shunting. Seventy-four percent (53/72 patients) with preoperative visual problems experienced postop visual improvement.[16] Zhang and colleagues reported 70% gross total resection in a total of 208

suprasellar NFPAs, and postoperative complications of diabetes insipidus (14%), CSF leak (5%) and 13% required subsequent trans-cranial craniotomy to completely remove tumor.

Tumor size and cavernous sinus invasion are factors that adversely impact the rate of gross total resection of NFPAs for all surgical approaches. Honegger et al reported that NFPAs with greater than 2 cm suprasellar extension and irregular or multilobulated shapes correlated with incomplete resections in 105 patients. Lamproulos et al reported 63% gross total resection in 97 NFPA patients, with cavernous sinus invasion, tumor size greater than 2.5 cm, and repeat operations correlated with worse outcomes. Postoperative visual improvement was found in 38% of patients and anterior pituitary function normalized in 14 of 75 patients, with improvement in 24 of 75 patients. In 1995, Greenman and colleagues reported significant postoperative anterior pituitary dysfunction in 68% of 26 NFPA patients who underwent transsphenoidal surgery. The same group reported a later 2003 study with a cohort of 122 NFPA patients that had gross total resection in 30 patients (25%) at 3 months, and showed that cavernous sinus invasion and suprasellar and infrasellar tumor extension were factors associated with diagnosis of tumor recurrence or progression at a mean of 51 months follow-up after surgery. Meij et al described the correlation of biopsy-proven dural invasion in 46 out of 81 patients correlated with tumor size and observation of residual tumor, but not associated with recurrence. Interestingly, Scheithauer described 23 cases of nonfunctioning corticotroph-staining pituitary tumors that were associated with higher residual tumor and tumor progression after surgery.

Alahmadi et al found that inadequate bony sphenoid and/or sellar exposure found during repeat transsphenoidal surgery likely limited the initial surgery, and expanded exposure resulted in gross total resection of the majority of NFPAs without cavernous sinus invasion. Mattozo et al also reported that suboptimal bony sphenoid exposure was found in 97% and suboptimal sellar exposure was found in 93% of patients needing repeat transsphenoidal surgery.

Use of lateral rhinotomy approach in 48 NFPA surgeries reported by Petruson et al was associated with only 1 recurrence on CT imaging at 5 years, 12% postoperative pituitary dysfunction, and 79% visual improvement.

Of note, the report from Abe et al describes successful gross total resection via staging of serial transsphenoidal resections of fibrous or dumbbell-shaped NFPAs in 7 of 8 patients over 5 months without complications. In a large series, Wilson reported a postoperative CSF leak rate of 4.3% in 530 patients despite the use of a lumbar drain.[29]

The safety and efficacy of NFPA transsphenoidal surgery in elderly patients were reported in 2 Class III studies. Benbow et al showed in 38 patients (greater than 64 years old) that perioperative complications were higher in the transcranial group (5 of 6 patients) compared to the transsphenoidal group (6 of 32 patients). Kurosaki and colleagues reported a 75% gross total resection rate via transsphenoidal approach in 32 elderly patients (greater than 70 years old) who meet the American Society of Anesthesia (ASA) criteria of grades 1-3 for surgery.[30] Visual disturbances were improved in 19 of 23 cases, and complications included 5 CSF leaks, transient oculomotor palsy in 1 patient, and new adrenocorticotropic deficit in 5 of 11 patients.[30]

Endoscopic Surgical Resection

NFPA surgery with endoscopic visualization is a more recent technological innovation. There are 14 reports offering Class III evidence in studies of endoscopic NFPA surgery (Table 1).[31-44]

Class III evidence is found in Jho and Carrau's 1997 report including 19 NFPA surgeries with 16 gross total resections, and 3 noted cavernous sinus residuals. Postoperative visual improvement was observed in all 11 patients showing preoperative impairment, and new hypopituitarism was found postop in 3 of 10 preoperatively normal patients.

In 2000, Shen et al retrospectively reported achieving gross total resection of 12 out of 15 endoscopic NFPA surgeries with visual improvement in all previously impaired patients. Lasio et al reported successful use of repeat surgery using endoscopic visualization with or without image guidance in 2002. In 2005, Kabil et al showed, at a mean follow-up of 38 months, 93% of 161 NFPA patients had no residual tumor after endoscopic surgery. Schwartz and colleagues reported on combining endoscopic tumor visualization and resection with iMRI guidance in 2006. Frank et al also reported gross total resection in 20 of 35 (60%) endoscopic NFPA resections. In 2008, Dehdashti et al reported on retrospective review of 200 consecutive endonasal endoscopic surgeries that included 111 NFPAs. Gross total resection was achieved in 98 of 111 patients, with 97% of patients without cavernous sinus invasion having complete resection. Full visual recovery was observed in 36 (57%) patients, partial visual recovery in 21 (34%) patients, and only 6% had no visual improvement. Three reports were released in 2010. Gondim et al showed 75% of 93 NFPA patients had a gross total resection via endoscopic surgery, with 10 patients achieving gross total resection at a second surgery. In contrast, Santos et al showed that endonasal endoscopic NFPA surgery only achieved gross total resection in 3 of 12 patients. Leach et al showed that additional technical experience from 15-30 months versus the early 0-15 months' experience was associated with decrease in operative time from 120 minutes to 90 minutes. Hwang et al reported a small series from Korea of gross total resection in 50% of 27 patients and improved vision in 79% of patients, with 2 patients suffering complications.

In 2014, Dallapiazza et al and Chone et al reported retrospective series of endoscopically resected NFPAs. Dallapiazza and colleagues showed 71% gross total resection with tumors less than 10 cc volume and Knosp grades of 0 to 2. Chone et al reported a small study of 30 patients with 94% gross total resection but 10% surgical complications, including 1 death, 2 carotid artery lesions, and 2 CSF leaks. In a large consecutive endoscopic surgery patient series, the Pittsburgh group reported 84% gross total resection in NFPAs without cavernous sinus invasion and 35% gross total resection in tumors with cavernous sinus invasion. Visual improvement was found in 81% of previously impaired patients. Gross total resection was lower at 74% in recurrent NFPAs without cavernous sinus invasion, and 19% in tumor recurrences with cavernous sinus invasion. Barazi et al reported using extended endoscopic transplanum-transtuberculum approach to achieve 40% (6 of 15 patients) gross total resection, and complications in 6 of 15 patients (2 CSF leaks, 1 chronic subdural hematoma, 1 epistaxis, 1 surgical hematoma, 1 capsular ischemia).

Comparisons between Transsphenoidal and Endoscopic Approaches

There are 5 studies with Class III evidence that compare the more recently developed endoscopic approach with microscopic transsphenoidal craniotomy for NFPA surgery, with most showing comparable efficacy but 1 study providing Class III evidence of cases in which

endoscopy was able to remove residual tumor left after microsurgery (Table 1).[45-49] Messerer et al studied 82 endoscopic surgeries performed by a single surgeon compared with 82 transsphenoidal surgeries performed mostly by the same surgeon and another surgeon at 1 year postoperative follow-up.[45] No difference in complications was observed, with 50% gross total resection achieved with transsphenoidal approach and 74% gross total resection achieved via endonasal endoscopic approach.

In 1999, Sheehan et al reported preliminary comparison of endonasal endoscopic approach (26 NFPAs) with sublabial microsurgical transsphenoidal approach (44 matched patients) that showed no significant differences in extent of resection, visual or endocrinological outcomes, or complications. The endoscopic group had significantly less operative time.[47] The University of Virginia group also found no significant differences in tumor resection extent or endocrine outcome between transsphenoidal and endoscopic cohorts, with higher intraoperative lumbar drain placement in 70% of microscopic resections versus 1.7% of endoscopic surgeries.[46] Chen's group reports a prospective series of 355 NFPA surgeries with mean 5.5-year follow-up that included both microscopic and endoscopic resections with 79.5% gross total resection rate.[49] McLaughlin et al showed that 46% (33 of 71 NFPAs) of patients had residual tumor identified via endoscopy after initial microsurgery, and further resection was performed in 88% (29 of 33 patients).[48]

Transcranial Approach

The transcranial approach is now usually an infrequently used alternative or complementary approach to transsphenoidal NFPA resection. One Class III report from Nielsen et al in 2007 compares 32 transcranial NFPA cases with 160 transsphenoidal approaches and showed that transcranial patients had significantly worse mental health and depression outcomes. No differences in endocrine complications, number of surgeries, and need for radiotherapy were found between the 2 groups.[50] Other studies all offered Class III evidence (Table 1). One report from van Lindert et al in 1991 describes a retrospective review of 53 patients who underwent only transcranial NFPA resection: 81% of 53 patients had symptomatic improvement, with a 6% surgical mortality rate. Thirty-six percent of patients thought to have gross total resections showed delayed tumor recurrence.[51]

Colao et al reported from 1- to 10-year follow-up on patients who underwent transsphenoidal or peritoneal craniotomies and combined with radiotherapy. Eighty-two percent of the 72 patients with subtotal resections underwent radiotherapy, and the incidence of hypopituitarism increased from 29% at 1 year to 92% at 10 years follow-up.[52]

In a large series of 721 patients (660 transsphenoidal, 61 transcranial surgeries), Nomikos et al reported normalization of preoperative pituitary deficits in 20% of transsphenoidal group versus none in the transcranial group. Deterioration of pituitary function was found in 1% of the transsphenoidal group versus 15% of the transcranial group.[53] Similar results were reported by Wichers-Rother et al in 2004: no improvement in pituitary function was observed in both the transsphenoidal (109 patients) and transcranial (21 patients) surgery groups, with postoperative endocrine dysfunction higher at 2 years in the latter group. Visual improvement and headache relief occurred in both groups, but was earlier in the transsphenoidal group.[54] Discussed above, Benbow et al showed in 1997 that elderly patients greater than 64 years old had fewer perioperative complications with transsphenoidal versus transcranial surgery.[55] The strategy of

simultaneous combined transsphenoidal and transcranial resections of NFPAs was described by Alleyne et al in 2002 and Leung et al in 2011 for small series of selected NFPAs.[56,57] Alleyne et al retrospectively reviewed 10 patients undergoing both transsphenoidal and pterional craniotomies for giant NFPAs, with 4 gross total resections and 2 near total resections. All 9 patients presenting with visual impairment improved, with 5 achieving full visual recovery. Complications of transient oculomotor palsy (n = 3), mild hemiparesis (n = 3), and postoperative seizures (n = 2) were reported. With the goal of dissecting giant NFPAs (greater than 4 cm in height) away from optic apparatus and vascular structures, Leung et al utilized subfrontal or anterior interhemispheric craniotomy approaches simultaneously with transsphenoidal resection in 11 patients.[57] They report 5 gross total resections, with 5 of 7 patients experiencing full visual recovery. Subsequently, 7 of 11 patients underwent radiotherapy due to residual or recurrent tumor.

Neuronavigation

The use of intraoperative neuronavigation has been utilized for endonasal transsphenoidal surgery with varying prevalence. This has been a transition from the use of fluoroscopy for localizing the sella. We identified 1 article (Class III) that fit the inclusion and exclusion criteria for the surgical resection of nonfunctioning pituitary adenomas (Table 2). Lasio et al reported their experience with neuronavigation in a cohort of 11 patients for recurrent pituitary adenomas resected via the endoscopic endonasal transsphenoidal approach.[32] They noted no difference in morbidity or mortality compared to a non-navigated (no fluoroscopy) control group. They did find longer set-up times, but shorter surgical and overall operating room times. They conclude that neuronavigation is a safe adjunct for transsphenoidal surgery and may result in faster operative times.

Intraoperative Imaging

The use of intraoperative imaging as an adjunct to transsphenoidal surgery has been necessary for safe and maximal resection of pituitary tumors since the 1960s.[58] With the advent of intraoperative CT and MRI, intraoperative imaging technologies were further advanced to allow the real-time capacity to identify residual disease. With the inclusion and exclusion criteria for this section, we identified one article (Class III) evaluating fluoroscopy and nonfunctioning adenoma resection. Seven Class III articles were identified for the evaluation of intraoperative MRI (any field strength) (Table 3). No articles were identified evaluating intraoperative CT imaging for nonfunctioning adenoma surgery.

In a retrospective study evaluating the long-term results of transsphenoidal surgery in which intraoperative fluoroscopy was routinely utilized, Ebersold et al demonstrated surgical mortality of 3%, 1 postoperative CSF leak repair (1%), and 2 patients requiring CSF diversion due to subarachnoid hemorrhage and hydrocephalus.[16] In tumors with suprasellar extension, subarachnoid air was injected via a lumbar puncture to facilitate descent of the tumor as well as fluoroscopic contrast.

Intraoperative MRI has been evaluated for nonfunctioning pituitary adenoma transsphenoidal surgery with both low-field (0.12-0.2T) and high-field (1.5T) devices. In a prospective study evaluating a 0.2T intraoperative MRI during transsphenoidal surgery, Fahlbusch et al reported the detection of residual disease in 27% of patients.[9] They concluded that iMRI improved overall

GTR from 43% to 70%. They also noted an approximately 30% rate of artifact obscuring imaging and a 16% false-positive rate.

A follow-up prospective study was performed by the same group evaluating the high-field intra-operative MRI (1.5T) in 106 patients with nonfunctioning pituitary adenomas.[59] The authors note that residual tumor was identified during surgery in 42% of patients. They concluded that iMRI (1.5T) improved overall GTR from 58% to 82%. The false positive rate was 5.7%.

Six additional Class III articles were identified supporting the role of intraoperative MRI and transsphenoidal surgery. Three of these articles studied low-field iMRI devices (0.12-0.15T), and 3 studied high-field devices (1.5T).[35,60-64] The overall rate of GTR at initial iMRI ranged from 36%-57% in the low-field studies and 44%-75% in the high-field studies. This improved to 82%-95% overall GTR in the low-field studies and 66% in the high-field study. There was a false positive rate of upwards of 64%.[63]

CSF Diversion

CSF diversion has been utilized with various purposes for transsphenoidal surgery. Primary applications include instillation of air for intraoperative pneumoencephalography, injection of volume to achieve suprasellar tumor descent, fluorescein injection for intraoperative CSF leak detection, and postoperative CSF diversion to augment the dural closure. For nonfunctioning pituitary adenomas, we identified 5 articles (Class III) that fit the inclusion and exclusion criteria (Table 4). Ebersold et al reported the use of preoperative lumbar puncture and instillation of air for pneumoencephalography.[16] They note a GTR rate of 84% and a postoperative CSF leak rate of 1%. Two articles demonstrated the utility of intrathecal saline injection to assist in tumor descent (20-80 mL).[17,65] They noted usefulness of saline injection in 70%-83% of tumor resections without catheter-related complications. Two articles reported the utility of perioperative CSF diversion to augment dural repair.[46,29] Wilson et al reported a 4.3% postoperative CSF leak rate with the use of CSF diversion. Dallapiazza reported a 12% rate of postoperative CSF leakage, with the majority of patients (70%) undergoing CSF diversion in their microscopic surgery cohort. Interestingly, they noted a 7% postoperative CSF leak rate in their endoscopic surgery cohort in which the CSF diversion utilization was in 1.7% of patients. This difference between cohorts was not statistically significant.

Dural Closure Techniques

There are numerous methods for dural closure following transsphenoidal microsurgery. These include allograft placement, autologous fat or fascia graft placement, rigid buttress placement, and pedicled, vascularized tissue transpositions. Little, however, has been reported specifically for nonfunctioning pituitary adenoma resection. With our inclusion and exclusion criteria, we identified only 1 article that discussed closure techniques (Table 5).[66] In their series, Jho and Carrau reported 19 cases that were closed with autologous fat grafts for CSF leaks or large post-resection cavities. The fat grafts were supported with bone when possible or with absorbable buttress when bone could not be placed. With this technique, 1 postoperative CSF leak (5.3%) was reported in a recurrent pituitary adenoma with a large post-resection cavity where bone could not be placed. The patient underwent reoperation, and the defect was repaired with a larger autologous fat graft. CSF diversion was not routinely used.

DISCUSSION

Transsphenoidal microsurgery as the choice for NFPAs has now been supplemented and, in some centers, replaced with experienced adoption of endoscopic NFPA resections. Due to comparative efficacy and safety, the choice of surgical approach and techniques continues to be determined based on surgeon experience, tumor characteristics, and patient selection. Intraoperative imaging has also been advanced by introduction of various forms of the sophisticated intraoperative MRI, although it is relatively costly and not feasible at all hospitals. The judicious selection of surgical strategies (single or combined approaches), along with appropriate use of neuronavigation, intraoperative imaging, and CSF diversion or repair techniques continue to benefit NFPA patients. These surgical methodologies will continue to be practiced, improved, and passed to the next generation of neurosurgeons.

CONCLUSION

Future Research

Analysis of the safety and efficacy of endoscopic-guided versus microsurgical approaches will likely be a focus of clinical research, with further studies on the impact of the learning curve and determining factors influencing the learning curve for new surgeons. Factors affecting surgery for NFPAs in the elderly would also be interesting and important to study for our population, with longer lifespans living with slow-growing benign pituitary tumors.

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FIGURES

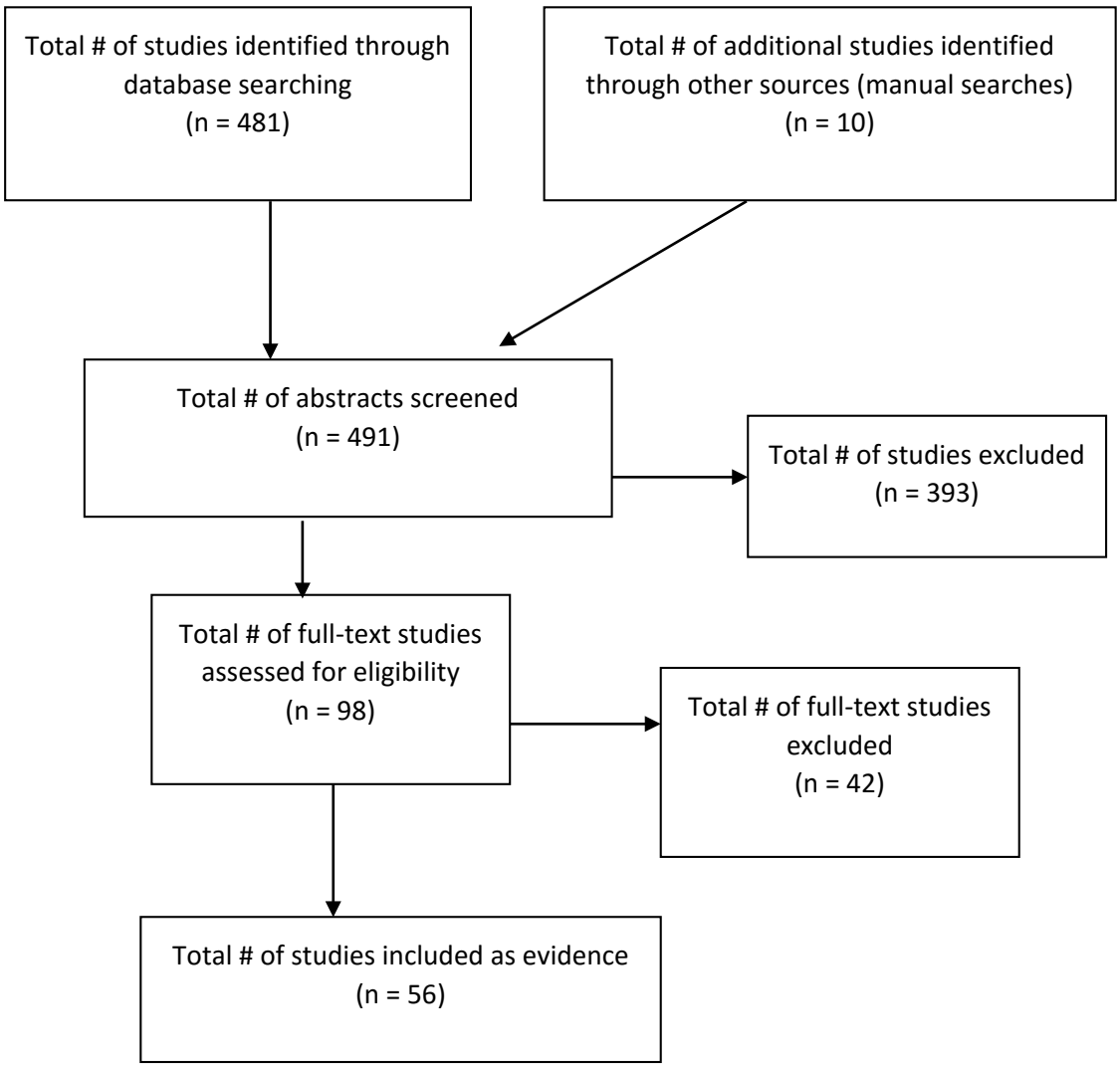

Figure 1: Article Flow Chart

TABLES

Table 1: Surgical Approach (endonasal, sublabial, micro, endo, craniotomy, etc).

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Nielsen EH, Lindholm J, Laurberg P, Bjerre P, Christiansen JS, Hagen C, Juul S, Jorgensen J, Kruse A, Stochholm K (2007)[50]	Retrospective review of 192 Danish NFPA patients who had surgery from 1985 to1996 (160 transsphenoidal approach vs 32 craniotomy approach) evaluating causes of death and quality of life based on questionnaire response.	Therapeutic / III	Among 109 (81%) patients who responded to the questionnaires (SF36 and MD-10 depression surveys), there was no difference in cardiovascular/cerebrovascular or cancer mortality between the transsphenoidal vs craniotomy groups. Univariate and multivariate analysis showed that craniotomy patients scored significantly worse in SF-36 mental health and mental components and had significantly higher median MDI scores (11.5 vs 5.78) for depression. No differences among the surgical groups were detected with regard to number of surgeries, pituitary insufficiency, pituitary apoplexy incidence, and radiotherapy. The retrospective design of this study renders it Class III evidence.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Kremer P, Forsting M, Ranaei G, Wüster C, Hamer J, Sartor K, Kunze S (2002)[12]	Assessment of immediate (within 3 days) postoperative MRI in assessing extent of resection	Diagnostic / III	Diagnostic study evaluating immediate postoperative MRI for detecting residual adenoma. Fifty patients underwent immediate (within 3 days) postoperative MRI following transsphenoidal resection of NF pituitary macroadenomas. Detection of residual adenoma on the immediate postoperative MRI was felt to be markedly hindered by blood products and adipose packing. Twenty-five (50%) patients were suspected of having residual tumor based on immediate MRI; however, delayed MRI studies at 3 months and 1 year demonstrated residual tumor in only 15 (30%) patients. The lack of blinded evaluation renders this Class III evidence.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C (2001)[9]	Assessment of extent of resection in 44pts with pituitary macroadenomas using intraoperative MRI	Therapeutic / III	Intraoperative 0.2T MRI was utilized in 44 patients undergoing transsphenoidal resection of pituitary macroadenomas. In 30% of patients, intraoperative MRI interpretation was felt to be limited by the presence of artifact. Among 33 patients with surgeon-estimated gross total resection, 9 (27%) had residual tumor detected by intraoperative MRI leading to further resection. Overall, intraoperative MRI increased the rate of complete surgical resection from 43% to 70% as confirmed by delayed MRI. False-positive results for intraoperative residual tumor were observed in 16% of patients. Although performed in a prospective manner, the lack of an appropriate control group renders this Class III evidence.
Yoon PH, Kim DI, Jeon P, Lee SI, Lee SK, Kim SH (2001)[13]	Assessment of immediate (within 7 days) postoperative MRI in assessing extent of resection	Diagnostic / III	Thirty-two patients underwent immediate (within 7 days) postoperative MRI following transsphenoidal resection of NFPA. Residual tumor was detected in eight patients based on nodular enhancement pattern and confirmed by delayed (6 months) MRI. The lack of an appropriate control group renders this Class III evidence.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Flitsch J, Spitzner S, Lüdecke DK (2000)[14]	Prospective study of emotional disturbances in forty-eight patients (11 with NFPA) who underwent transsphenoidal resection of pituitary adenomas	Therapeutic / III	Emotional disorders were assessed in 11 patients with NFPA before and after transsphenoidal resection. Fatigue, depression, and excitability were the most common emotional disorders reported on preoperative interview. Following resection, the majority of patients reported an increase in physical wellbeing at 6 months postoperatively. The lack of an appropriate control group renders this Class III evidence.
Lillehei KO, Kirschman DL, Kleinschmidt-DeMasters BK, Ridgway EC (1998)[15]	Prospective study evaluating rate of tumor recurrence following gross total resection of NFPA by the transsphenoidal approach	Therapeutic / III	Gross total resection of non-functioning pituitary macroadenomas was achieved in 38 of 45 patients (84%) via transsphenoidal surgery. Subsequent radiotherapy was not performed in 32 patients. Serial radiographic assessment revealed a 6% 5-year recurrence rate. Recurrence occurred in 2 patients, who were both successfully treated using radiation therapy (1 required repeat operation). The lack of an appropriate control group renders this Class III evidence.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Jho HD, Carrau RL (1997)[66]	Initial assessment of clinical outcomes following endoscopic endonasal transsphenoidal resection of 50 sellar lesions (19 NFPA)	Therapeutic / III	Early assessment of 50 patients who underwent endoscopic endonasal transsphenoidal surgery. Among 19 patients with NFPA, gross total resection was achieved in 16 patients (84%), with cavernous sinus residual noted in 3 patients. Postoperative visual improvement was observed in all 11 patients presenting with impairment. New hypopituitarism was observed in 3 of 10 patients (30%) with normal preoperative anterior pituitary function. The lack of an appropriate control group renders this Class III evidence.
Kremer P, Forsting M, Hamer J, Sartor K (1996)[11]	Prospective observational study assessing the ability of postoperative MRI to detect residual tumor following NFPA resection	Diagnostic / III	Diagnostic study evaluating the ability of MRI to detect residual tumor in 22 patients with NFPA following transsphenoidal resection. Residual tumor was detected in 11 patients (50%) at 3 months postoperatively (n = 4 suprasellar; n = 5 parasellar; n = 2 retrosellar). No progression of residual tumor was observed over a 2-year radiographic follow-up. The lack of blinded evaluation renders this a Class III diagnostic study.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Arita K, Uozumi T, Yano T, Kurisu K, Hirohata T, Eguchi K, Tominaga A, Pant B, Iida K, Kawamoto H (1996)[10]	Assessment of postoperative gonadal function following transsphenoidal resection of pituitary adenomas in premenopausal women	Therapeutic / III	Preoperative menstrual disturbance was observed in 15 of 19 (79%) of women with NFPA. Following transsphenoidal resection, regular menstruation was restored in 7 (46%) women. Gonadotropin secretion returned to normal in 2 of 7 patients with baseline disturbance, while 4 of 6 patients with preoperative elevations of prolactin achieved normalization. The lack of an appropriate control group renders this study Class III evidence.
Messerer M, De Battista JC, Raverot G, Kassis S, Dubourg J, Lapras V, Trouillas J, Perrin G, Jouanneau E (2011)[45]	Retrospective case series comparing the sublabial microscopic approach to the endonasal endoscopic approach (82 cases done by surgeon A) for resection of NFPA	Therapeutic / III	Eighty-two microscopic surgeries were performed by 2 surgeons (A, B) compared to 82 endoscopic surgeries performed by a single surgeon (A). At 1-year postoperative interval, gross total resection was observed in 50% of patients utilizing the sublabial microscope approach compared to 74% utilizing the endonasal endoscopic approach. No significant difference in postoperative complications was observed. The retrospective design of the study and lack of blinded evaluation renders this Class III evidence.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Dallapiazza R, Bond AE, Grober Y, Louis RG, Payne SC, Oldfield EH, Jane JA Jr (2014)[46]	Retrospective comparison of surgical outcomes following endoscopic vs microscopic resection of Knosp grade 0-2 NFPA	Therapeutic / III	Comparison of the microscopic and endoscopic transsphenoidal cohorts revealed no significant differences in extent of resection or endocrinologic complications. Intraoperative placement of lumbar drains were used more commonly with the microscopic approach (70%) compared to the endoscopic approach (1.7%), although no significant difference in postoperative CSF leakage (12% vs 7%) was observed.
Dallapiazza RF, Grober Y, Starke RM, Laws ER Jr, Jane JA Jr (2014)[42]	Retrospective analysis of clinical and radiographic outcomes following endoscopic resection of NFPA with at least 5 years of follow-up	Therapeutic / III	The overall rate of GTR was 71% with NFPA with Knosp grade 0-2 and tumor volume <10 cc more likely to result in GTR. The observed recurrence rate following GTR was 12% with an overall progression rate of 61% observed following subtotal resection, although only 17% required further surgical intervention. Knosp grade was the only independent predictive factor associated with subtotal resection.
Chone CT, Sampaio MH, Sakano E, Paschoal JR, Garnes HM, Queiroz L, Vargas AA, Fernandes YB, Honorato DC, Fabbro MD, Guizoni H, Tedeschi H (2014)[43]	Retrospective analysis of 30 patients with NFPA following endoscopic resection	Therapeutic / III	Small study (N = 30) demonstrating a GTR of 94% for NFPA using endoscopic transsphenoidal resection. Surgical complications occurred in 10% of patients, including 2 carotid artery lesions, 2 cerebrospinal fluid leaks, and 1 death.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Paluzzi A, Fernandez-Miranda JC, Tonya Stefko S, Challinor S, Snyderman CH, Gardner PA (2014)[44]	Retrospective review of clinical and radiographic outcomes in 550 patients who underwent endoscopic resection of NFPA	Therapeutic / III	Among NFP macroadenomas without cavernous sinus (CS) invasion, GTR was achieved in 84% and near-total resection (NTR) in 9%. Visual impairment improved in 82%. Among NFP macroadenomas with CS invasion, GTR was achieved in 35% and NTR in 42%. Visual impairment improved in 81%. For all NFPA, the rate of GTR was 65.3%, NTR 20%, and visual impairment improvement was 82%. Among recurrent adenomas, the rate of GTR was 45%, with GTR achieved in 74% of patients with macroadenomas without CS invasion (n = 34) and 19% with CS invasion (n = 37)
McLaughlin N, Eisenberg AA, Cohan P, Chaloner CB, Kelly DF (2013)[48]	Retrospective case series of 140 pituitary tumors, including 71 NFPA, that underwent endoscopic visualization after initial microscopic resection. Residual tumor identified in overall 40% (56/140), leading to further resection in 36% (50/140 cases)	Therapeutic / III	Among NFPA, residual adenoma found on endoscopy in 46% (33/71) of patients with further resection utilizing endoscopic visualization performed in 29/33 (88%)
Barazi SA, Pasquini E, D'Urso PI, Zoli M, Mazzatenta D, Sciarretta V, Frank G (2013)[40]	Retrospective review of 22 extended endoscopic transplanum-transtuberculum approach (ETTA) procedures in 19 patients, including 15 NFPA	Therapeutic / III	Six (40%) of 15 NFPA patients had GTR. Complications occurred in 6/15 (40%) patients, including 2 CSF leaks, 1 chronic subdural hematoma, 1 episode of epistaxis, 1 surgical cavity hematoma, and 1 capsular ischemia.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Hwang JM, Kim YH, Kim JW, Kim DG, Jung HW, Chung YS (2013)[41]	Retrospective evaluation of 27 patients with NFPA who underwent repeat endoscopic transsphenoidal resection following prior microscopic transsphenoidal resection	Therapeutic / III	GTR was achieved in 50% of patients, with a mean volumetric extent of resection of 90%. Vision improvement occurred in 79%, while 2 patients experienced complications from the endoscopic surgery.
Lampropoulos KI, Samonis G, Nomikos P (2013)[27]	Retrospective evaluation of 184 patients, including 97 NFPA patients, who underwent microscopic transsphenoidal resection	Therapeutic / III	GTR was achieved in 63%. Factors associated with subtotal resection and overall worsened outcome included cavernous sinus invasion, tumor size >25 mm, and reoperation. Visual improvement occurred in 21/55 (38%). Endocrinologic evaluation demonstrated normalization of anterior pituitary function in 14/75 and improvement in 24/75. Anterior pituitary function remained unchanged in 36/75.
Alahmadi H, Dehdashti AR, Gentili F (2012)[23]	Retrospective review of 39 (19 NFPA) patients with residual or recurrent pituitary tumors after prior microscopic surgery.	Therapeutic / III	Limitations of prior microscopic resection included inadequate sphenoid or sellar exposure in 30/39 (77%) cases. Gross total resection was achieved in 6 of 7 recurrent NFPA without cavernous sinus invasion. Subtotal resection in 12/19 recurrent NFPA with cavernous sinus invasion.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Chen L, White WL, Spetzler RF, Xu B (2011)[49]	Prospective case series of 355 NFPA with mean follow-up period of 5.5 years including patients who underwent microscopic transsphenoidal resection and endoscopic-assisted transsphenoidal resection	Therapeutic / III	Overall gross total resection in 306 (79.5%). No comparison of outcomes among microscopic vs endoscopic-assisted transsphenoidal resection.
Leung GK, Law HY, Hung KN, Fan YW, Lui WM (2011)[57]	Retrospective series of 11 patients with NFPA who underwent simultaneous supratentorial (subfrontal or anterior interhemispheric) craniotomy and sublabial transsphenoidal resection of large and giant macroadenomas	Therapeutic / III	Among NFPA >4 cm in height, 5/11 (45%) had GTR, with 5 of 7 patients experiencing full visual field recovery. Seven patients underwent subsequent radiotherapy. The supratentorial craniotomy was found helpful for dissection from the optic and vascular structures and delivering the tumor down into the sella.
Gondim JA, Schops M, de Almeida JP, de Albuquerque LA, Gomes E, Ferraz T, Barroso FA (2010)[37]	Retrospective review of 228 consecutive patients (93 NFPA; 3 cm mean size) following endoscopic transsphenoidal resection with mean follow-up period of 61 months.	Therapeutic / III	Among 93 NFPA, 70 (75%) achieved gross total resection. Ten patients required a second surgery for additional resection for an overall 83% remission rate.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Leach P, Abou-Zeid AH, Kearney T, Davis J, Trainer PJ, Gnanalingham KK (2010)[38]	Retrospective series of 67 NFPA comparing clinical and radiographic outcomes between early (0-15 months) and delayed (15-30 months) experience utilizing endoscopic transsphenoidal resection	Therapeutic / III	Additional experience with endoscopic transsphenoidal resection leads to decreased operative times (120 minutes vs 90 minutes).
Santos AR, Fonseca Neto RM, Veiga JC, Viana Jr J, Scaliassi NM, Lancellotti CL, Lazarini PR (2010)[39]	Retrospective review of 30 consecutive (12 NFPA) endonasal endoscopic surgeries	Therapeutic / III	Gross total resection was achieved in 3/12 NFPA and <80% resection in 6/12 patients.
Dehdashti AR, Ganna A, Karabatsou K, Gentili F (2008)[36]	Retrospective review of 200 consecutive endonasal endoscopic surgeries (111 NFPA)	Therapeutic / III	Endonasal endoscopic approach is successful and safe with median 22 month follow-up (range 4-34 months). GTR was achieved in 98/111 (88%) of NFPA. Among patients without cavernous sinus invasion, 97% had gross total resection. Full visual field (VF) recovery was observed in 36 (57%) patients, while partial VF was observed in 21 (34%) patients. Only 6 (9%) patients had no VF recovery.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Honegger J, Ernemann U, Psaras T, Will B (2007)[24]	Prospective case series of 105 NFPA who underwent transsphenoidal removal of NFPA to determine MRI characteristics favorable for transsphenoidal resection	Therapeutic / III	Eighty-seven of 105 (83%) patients with NFPA with suprasellar extension underwent surgical intervention via a transsphenoidal approach. Statistically significant MRI predictors of incomplete resection included tumors with >2 cm suprasellar extension and multilobulated or irregular shape.
Schwartz TH, Stieg PE, Anand VK (2006)[35]	Retrospective review of 15 (11 NFPA, 3 acromegaly, 1 resistant PRL) patients who underwent endoscopic transsphenoidal surgery with low-field 0.12T iMRI.	Therapeutic / III	iMRI demonstrated residual tumor in 3 patients with NFPA leading to further endoscopic resection of tumor. In patients with 4 NFPA, iMRI suggested the presence of residual adenoma; however, further endoscopic evaluation revealed these to be normal postoperative changes.
Frank G, Pasquini E (2006)[34]	Retrospective review of 35 NFPA with cavernous sinus invasion who underwent endoscopic endonasal resection from the cavernous sinus between 1998 and 2005.	Therapeutic / III	Among 35 NFPA patients with cavernous sinus invasion, 20 (60%) had their tumor completely resected, with an additional 9 (25.5%) patients achieving subtotal resection.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Mattozo CA, Dusick JR, Esposito F, Mora H, Cohan P, Malkasian D, Kelly DF (2006)[25]	Retrospective review of 30 (16%) of 188 consecutive NFPA patients who had repeat transsphenoidal surgery via a repeat transsphenoidal approach.	Therapeutic / III	Initial transsphenoidal resection was performed via the sublabial approach in 23 (77%) patients, while 6 patients had an endonasal approach and 1 had a lateral rhinotomy approach. Anatomic factors felt to contribute to the need for repeat surgery included suboptimal bony sphenoid keel (97%) and sella (93%) removal. Residual adenoma >1 cm also contributed to the need for repeat surgery.
Kabil MS, Eby JB, Shahinian HK (2005)[33]	Retrospective case review of 161 NFPA patients who underwent endoscopic transsphenoidal resection	Therapeutic / III	At a mean follow-up time of 38 months, 149/161 (93%) patients showed no evidence of residual tumor.
Nomikos P, Ladar C, Fahlbusch R, Buchfelder M (2004)[53]	Comparison of transsphenoidal vs transcranial surgery on endocrine outcome	Therapeutic / III	Analysis of endocrinologic outcome for 721 patients who underwent transsphenoidal (n = 660) or transcranial (n = 61) removal of an NFPA demonstrated improved anterior pituitary function following transsphenoidal resection. Preoperative deficits were present in approximately 85% of both groups, with normalization of pituitary function observed in 20% of the transsphenoidal group postoperatively compared to 0% in the transcranial group. Any improvement in pituitary function was observed in 30% vs 11%, respectively. Deterioration of pituitary function was noted in 1% vs 15%.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Wichers-Rother M, Hoven S, Kristof RA, Bliesener N, Stoffel-Wagner B (2004)[54]	Comparison of transsphenoidal vs transcranial surgery on endocrine and clinical (headache, visual) outcome	Therapeutic / III	Analysis of endocrinologic outcome for 130 patients who underwent transsphenoidal (n = 109) or transcranial (n = 21) removal of a non-functioning macroadenoma. No improvement in anterior pituitary function following resection was observed in either group. Postoperative deficits in the adrenal and thyroid axes were significantly increased at 2 years in the transcranial resection cohort. Significant visual improvement was observed in both groups, with earlier (within 3 months) improvement more frequent following transsphenoidal resection. Similarly, improvement in headache symptoms occurred in both groups, with earlier improvement observed in the transsphenoidal cohort.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Greenman Y, Ouaknine G, Veshchev I, Reider-Groswasser II, Segev Y, Stern N (2003)[28]	Evaluation of characteristics associated with postoperative tumor progression and recurrence following transsphenoidal resection of NF pituitary macroadenomas	Therapeutic / III	One hundred twenty-two patients with nonfunctioning macroadenomas underwent transsphenoidal resection. Gross total tumor removal was achieved in 30 (25%) patients based on 3-month follow-up MRI. With a mean follow-up time of 51 months, subsequent tumor enlargement occurred in 41/78 (53%) patients with radiographic residual tumor and in 6/30 (20%) patients without apparent residual tumor at 3 months. Factors associated with tumor progression included increased suprasellar and infrasellar extension of the residuum and cavernous sinus invasion.
Lasio G, Ferroli P, Felisati G, Broggi G (2002)[32]	Assessment of image guidance for endoscopic resection of recurrent pituitary adenomas	Therapeutic / III	Surgical morbidity and operative time were assessed in 19 patients undergoing re-resection of recurrent pituitary adenomas. Image guidance was utilized in 11 patients with no significant difference in extent of resection or morbidity between the 2 cohorts. Mean OR setup time was 13 minutes faster in the non-image guided procedures, while operative time was 36 min shorter with image guidance.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Alleyne CH Jr, Barrow DL, Oyesiku NM (2002)[56]	Assessment of extent of resection and clinical outcomes using a simultaneous combined transsphenoidal and transcranial approach for resection of giant pituitary adenomas	Therapeutic / III	Retrospective review of 10 patients undergoing simultaneous transsphenoidal and transcranial (pterional approach) resection of giant pituitary adenomas. Gross total resection was achieved in 4/10 patients with near total resection in an additional 2 patients. Visual improvement occurred in all patients presenting with impairment (n = 9). Complete visual recovery occurred in 5 of 9 patients at 6-month follow-up. Complications included transient oculomotor nerve palsy (n = 3) and mild hemiparesis (n = 3). Postoperative seizures occurred in 2 patients, and 1 patient expired secondary to pulmonary embolism at 3 months postoperatively. No cases of cranial infection were observed.
Meij BP, Lopes MB, Ellegala DB, Alden TD, Laws ER Jr. (2002)[18]	Comparison of tumor progression following transsphenoidal resection of pituitary adenomas with and without dural invasion	Therapeutic / III	Three hundred fifty-four patients underwent transsphenoidal resection of pituitary adenomas with sampling of the sellar dura for tumor invasion. Evidence of dural invasion was present in 46 of 81 (57%) patients with NFPA, with the frequency of dural invasion increased in accordance with tumor size. Dural invasion was significantly associated with the presence of residual tumor following transsphenoidal resection, although recurrence following apparent gross total resection was not associated with dural invasion.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, Meyer FB, Laws ER Jr, Young WF Jr (2000)[19]	Retrospective analysis of clinical outcomes following transsphenoidal resection of clinically silent corticotroph adenomas	Therapeutic / III	Twenty-three cases of clinically silent corticotroph-staining adenomas were reviewed. All cases were associated with absence of any clinical signs of Cushing's syndrome and normal cortisol levels. Tumors were associated with a high rate of residual tumor or progression following resection.
Kurosaki M, Lüdecke DK, Flitsch J, Saeger W (2000)[30]	Retrospective evaluation of safety and efficacy of transsphenoidal resection of NFPA in elderly (>70 years) patients	Therapeutic / III	Transsphenoidal resection of NFPA was performed in 32 patients >70 years of age. Complete surgical removal was achieved in 24 (75%) cases. Visual disturbances were improved in 19 of 23 (83%) patients with preoperative visual impairment. Complications included new adrenocorticotropic impairment in 5 of 11 (45%) patients, transient oculomotor nerve palsy in 1 patient, and CSF leakage in 5 (16%) patients (2 requiring reoperation). Patients with American Society of Anesthesiologists (ASA) Grade 4 and 5 were excluded from this study and not considered candidates for surgery.
Shen CC, Wang YC, Hua WS, Chang CS, Sun MH (2000)[31]	Retrospective evaluation of clinical outcomes following endoscopic transsphenoidal resection of pituitary adenomas	Therapeutic / III	Fifteen patients with NFPA underwent resection via an endoscopic transsphenoidal approach. Gross total resection was achieved in 12 of 15 patients (80%). Visual improvement was noted in all patients with preoperative disturbance and no complications were reportedly encountered.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Zhang X, Fei Z, Zhang J, Fu L, Zhang Z, Liu W, Chen Y (1999)[17]	Retrospective assessment of extent of resection following transsphenoidal resection of NFPA with suprasellar extension with use of a lumbar drain catheter for intraoperative saline administration	Therapeutic / III	Gross total removal of adenoma was achieved in 146 of 208 (70%) patients with NFPA with suprasellar extension using the transsphenoidal approach. Resection of suprasellar tumor was facilitated by injection of 20-80 mL of saline solution and the sella packed with adipose or muscle tissue to prevent CSF leakage. Postoperative complications occurred in 48 (23%) patients, most commonly diabetes insipidus (14%) and CSF leakage (5%). Twenty-seven patients required craniotomy for further tumor resection.
Sheehan MT, Atkinson JL, Kasperbauer JL, Erickson BJ, Nippoldt TB (1999)[47]	Comparison of clinical outcomes following endoscopic resection of NFPA vs sublabial transseptal approach	Therapeutic / III	Retrospective review of 26 patients with NFPA who underwent endoscopic resection compared to 44 matched control patients who underwent transsphenoidal resection via sublabial transseptal approach. No significant difference in extent of resection, visual or endocrinologic outcome, or surgical complications were detected between the 2 surgical groups. The endoscopic approach was associated with a significantly decreased operative time (2.7 vs 3.4 hours). Septal complications occurred in 2 patients treated with the sublabial transseptal approach. No sinonasal complications were reported in the endoscopic group.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Colao A, Cerbone G, Cappabianca P, Ferone D, Alfieri A, Di Salle F, Faggiano A, Merola B, de Divitiis E, Lombardi G (1998)[52]	Long-term assessment of tumor control, endocrine function, and visual recovery following resection of NFPA via either the transsphenoidal or pterional approach.	Therapeutic / III	Eighty-four patients with NFPA were followed for 1-10 years' follow-up. Transsphenoidal resection of NFPA was performed in 69 patients, and resection using a pterional approach was performed in 15 patients. Complete surgical removal was achieved in 14% of patients, and postoperative radiotherapy was performed in 82% of patients with incomplete tumor removal. No significant difference in tumor regrowth was detected between irradiated and nonirradiated patients. The prevalence of hypopituitarism following radiotherapy increased from 29% at 1 year to 92% at 10 years' follow-up. Visual deterioration occurred in only 1 patient following radiotherapy.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Abe T, Iwata T, Kawamura N, Izumiyama H, Ikeda H, Matsumoto K (1997)[20]	Evaluation of staged transsphenoidal resection in 7 patients with non-functioning pituitary macroadenomas	Therapeutic / III	Staged transsphenoidal resection was performed in 7 patients with fibrous or dumbbell-shaped NF resulting in residual suprasellar adenoma following initial resection. Serial postoperative MRI were performed in 2-week intervals following initial resection with descent of the residual tumor into the sella observed within 2 months in 5/7 patients. Partial descent was observed in an additional patient by 3 months. Re-resection was performed within 5 months in all patients, with gross total resection achieved in 6 of 7 patients using a staged approach. No complications were reportedly encountered.
Benbow SJ, Foy P, Jones B, Shaw D, MacFarlane IA (1997)[55]	Retrospective assessment of clinical outcomes following transsphenoidal and transcranial resection of pituitary adenomas in the elderly (>64 years)	Therapeutic / III	Visual outcomes and perioperative complications were assessed in 38 elderly patients (>64 years of age) with pituitary adenomas (37 NFPA). Transsphenoidal resection was performed in 32 patients and transcranial resection in 6 patients. Perioperative complications were significantly more frequent in the transcranial group (5/6) compared to the transsphenoidal group (6/32).

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Young WF Jr, Scheithauer BW, Kovacs KT, Horvath E, Davis DH, Randall RV (1996)[21]	Retrospective review of clinical outcomes of 100 patients with non-secretory gonadotroph adenomas.	Therapeutic / III	One hundred patients with non-secretory gonadotropin-producing adenomas were randomly selected for review. Transsphenoidal resection was performed in 98 patients and transcranial resection in 2 patients. Gross total removal was reported in 90% of cases, although residual or recurrent tumor was observed in 42% of patients with at least 5-year follow-up based on CT imaging. One death occurred due to intracerebral hemorrhage, and new hypopituitarism developed postoperatively in 24% of patients.
Greenman Y, Tordjman K, Kisch E, Razon N, Ouaknine G, Stern N (1995)[22]	Comparison of anterior pituitary function preoperatively and postoperatively in patients with NFPA and growth-hormone secreting adenomas	Therapeutic / III	Anterior pituitary function was compared in NFPA (n = 26) vs GH-secreting adenomas (n = 15). Preoperative endocrine disturbances (other than GH levels) were significantly more frequent in patients with NFPA compared to acromegalics, with the prevalence unrelated to tumor size or extension. Postoperative anterior pituitary deficiency remained significantly increased in NFPA patients (68% vs 17%).
Petruson B, Jakobsson KE, Elfverson J, Bengtsson BA (1995)[26]	Retrospective study of 48 patients with NFPA who underwent resection using a lateral rhinotomy incision with at least 5 years of follow-up	Therapeutic / III	Using the lateral rhinotomy transsphenoidal approach, 1 tumor recurrence was observed by CT imaging at 5 years. New pituitary dysfunction occurred in 12% of patients while visual improvement was noted in 79%.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
van Lindert EJ, Grotenhuis JA, Meijer E (1991)[51]	Retrospective evaluation of 53 patients who underwent craniotomy for resection of NFPA	Therapeutic / III	Among 53 patients who underwent transcranial resection of NFPA, symptomatic improvement occurred in 81% of patients and 6% surgical mortality rate. Of patients who were felt to have undergone gross total resection, 36% had delayed recurrence.
Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986)[16]	Retrospective analysis of 100 patients with NFPA who underwent surgical resection with median follow-up period of 73 months	Therapeutic / III	Transsphenoidal surgery was performed in 100 patients with NFPA with use of intraoperative fluoroscopy in all cases. Surgically related mortality was 3%. One postoperative CSF leak required repeat surgery, while 2 patients required permanent CSF diversion for acquired hydrocephalus related to subarachnoid hemorrhage. Among the 72 patients who presented with visual impairment, 53 had improvement and 3 had visual worsening related to the surgery. 84% GTR.

Table 2: Neuronavigation

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Lasio G, Ferroli P, Felisati G, Broggi G. (2002)[32]	Assessment of image guidance for endoscopic resection of recurrent pituitary adenomas	Therapeutic / III	Surgical morbidity and operative time were assessed in 19 patients undergoing re-resection of recurrent pituitary adenomas. Image guidance was utilized in 11 patients with no significant difference in extent of resection or morbidity between the 2 cohorts. Mean OR setup time was 13 minutes faster in the non-image guided procedures while operative time was 36 minutes shorter with image guidance.

Table 3: Intraoperative Imaging (fluoro, MRI, CT)

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Nimsky C, von Keller B, Ganslandt O, Fahlbusch R (2006)[59]	Prospective case series of 106 NFPA patients received microscopic transsphenoidal resection with endoscopic assistance and intraoperative MRI.	Therapeutic / III	iMRI improved gross total resection from 58% to 82%. Initial iMRI revealed residual adenoma in 57 patients. Among patients who were expected to achieve GTR, 36/85 patients had residual at first iMRI. Further resection led to GTR in 71/85 of this patient subset. The lack of an appropriate control group renders this Class III evidence.
Fahlbusch R, Ganslandt O, Buchfelder M, Schott W, Nimsky C (2001)[9]	Assessment of extent of resection in 44 patients with pituitary macroadenomas using intraoperative MRI	Therapeutic / III	Intraoperative 0.2T MRI was utilized in 44 patients undergoing transsphenoidal resection of pituitary macroadenomas. In 30% of patients, intraoperative MRI interpretation was felt to be limited by the presence of artifact. Among 33 patients with surgeon-estimated gross total resection, 9 (27%) had residual tumor detected by intraoperative MRI, leading to further resection. Overall, intraoperative MRI increased the rate of complete surgical resection from 43% to 70% as confirmed by delayed MRI. False-positive results for intraoperative residual tumor were observed in 16% of patients. The lack of an appropriate control group renders this Class III evidence.

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Berkmann S, Schlaffer S, Nimsky C, Fahlbusch R, Buchfelder M (2014)[60]	Retrospective analysis of long-term (median 5.6 years) outcomes following transsphenoidal resection of NFPA with use of the intraoperative MRI	Therapeutic / III	Overall observed rate of GTR was 66%, which increased from 44% at time of initial iMRI scan. iMRI had sensitivity and specificity of 100% for detecting residual adenoma compared to use of the endoscope which demonstrated a sensitivity of 21% and specificity of 78%. A 7% recurrence rate among patients with GTR was observed and a 14% progression rate among patients with subtotal resection. 79% of tumor growth occurred within 5 years of resection. The rate of new hypopituitarism was 26%.
Hlavica M, Bellut D, Lemm D, Schmid C, Bernays RL (2013)[62]	Retrospective series of 104 NFPA patients utilizing 0.15T ultra-low field intraoperative MRI	Therapeutic / III	iMRI revealed GTR in 56/114 (53.8%) patients via iMRI following initial resection. Among patients (n = 48) with detected residual, 43 (41.3%) had further tumor removal verified by subsequent iMRI. Five patients were deemed to have unresectable residual tumor. Patients received 2.3 ± 1 iMRIs (range 2-8 iMRI). 11 out of 114 total patients had residual tumor at the end of surgery.

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Berkmann S, Schlaffer S, Buchfelder M (2013)[63]	Retrospective analysis of residual NFPA tumor volumes comparing intraoperative MRI to delayed MRI findings	Therapeutic / III	Comparison of intraoperative MRI tumor remnant volumes with 3-month delayed MRI volumes demonstrated tumor remnant volume reduction in 50% with complete resolution of the remnant in 64%. No change in tumor volume remnant was observed on MRI performed at 3 months and 1 year postoperatively.
Berkmann S, Fandino J, Muller B, Kothbauer KF, Henzen C, Landolt H (2012)[61]	Retrospective case series 114 NFPA including 79 patients (69%) who had surgery using 0.15T iMRI.	Therapeutic / III	iMRI improved gross total resection (GTR) rates. Initial iMRI determined 45 (57%) with GTR. Among patients with detected residual (n = 34), 31 had additional resection with overall GRT achieved in 65 (82%) patients based on postoperative MRI.
Berkmann S, Schlaffer S, Nimsky C, Fahlbusch R, Buchfelder M (2014)[64]	Retrospective case series 109 NFPA undergoing surgery using 1.5T iMRI	Therapeutic /III	On the initial iMRI scans, GTR was confirmed in 19 (17%) patients. Additional resection was possible in 62 (67%) patients, resulting in a significant volume reduction and increased GTR rate (49%). After additional resection for 69% of the procedures, the GTR rate on postoperative MRI was 75%.

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Schwartz TH, Stieg PE, Anand VK (2006)[35]	Retrospective review of 15 (11 NFPA, 3 acromegaly, 1 resistant PRL) patients who underwent endoscopic transsphenoidal surgery with low-field 0.12T iMRI.	Therapeutic / III	iMRI demonstrated residual tumor in 3 patients with NFPA leading to further endoscopic resection of tumor. In patients with 4 NFPA, iMRI suggested the presence of residual adenoma; however, further endoscopic evaluation revealed these to be normal postoperative changes.
Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986)[16]	Retrospective analysis of 100 patients with NFPA who underwent surgical resection with median follow-up period of 73 months.	Therapeutic / III	Transsphenoidal surgery was performed in 100 patients with NFPA with use of intraoperative fluoroscopy in all cases. Surgically related mortality was 3%. One postoperative CSF leak required repeat surgery while 2 patients required permanent CSF diversion for acquired hydrocephalus related to subarachnoid hemorrhage. Among the 72 patients who presented with visual impairment, 53 had improvement and 3 had visual worsening related to the surgery. 84% GTR.

Table 4: Use of CSF Diversion

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Dallapiazza R, Bond AE, Grober Y, Louis RG, Payne SC, Oldfield EH, Jane JA Jr (2014)[46]	Retrospective comparison of surgical outcomes following endoscopic vs microscopic resection of Knosp grade 0-2 NFPA	Therapeutic / III	Comparison of the microscopic and endoscopic transsphenoidal cohorts revealed no significant differences in extent of resection or endocrinologic complications. Intraoperative placement of lumbar drains was used more commonly with the microscopic approach (70%) compared to the endoscopic approach (1.7%), although no significant difference in postoperative CSF leakage (12% vs 7%) was observed.
Zhang X, Fei Z, Zhang J, Fu L, Zhang Z, Liu W, Chen Y (1999)[17]	Retrospective assessment of extent of resection following transsphenoidal resection of NFPA with suprasellar extension with use of a lumbar drain catheter for intraoperative saline administration	Therapeutic / III	Gross total removal of adenoma was achieved in 146 of 208 (70%) of patients with NFPA with suprasellar extension using the transsphenoidal approach. Resection of suprasellar tumor was facilitated by injection of 20-80 mL of saline solution and the sella packed with adipose or muscle tissue to prevent CSF leakage. Postoperative complications occurred in 48 (23%) patients, most commonly diabetes insipidus (14%) and CSF leakage (5%). Twenty-seven patients required craniotomy for further tumor resection.

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Saito K, Kuwayama A, Yamamoto N, Sugita K (1995)[65]	Retrospective study of 100 NFPA patients with suprasellar extension evaluating utility of lumbar drain placement and saline/lactated Ringer's injection	Therapeutic / III	Lumbar drain injection of fluid (NS or LR) is helpful in resecting tumors with suprasellar extension in 60/72 adenomas (83%). Adenomas with >30 mm suprasellar extension were much more difficult to remove completely (one exception which was performed in a staged manner).
Wilson CB (1992)[29]	Retrospective analysis of a large series of NFPA following transsphenoidal resection	Therapeutic / III	Postoperative CSF leakage occurred in 23 patients (4.3%) despite lumbar drain placement.
Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986)[16]	Retrospective analysis of 100 patients with NFPA who underwent surgical resection with median follow-up period of 73 months.	Therapeutic / III	Transsphenoidal surgery was performed in 100 patients with NFPA with use of intraoperative fluoroscopy in all cases. Surgically related mortality was 3%. One postoperative CSF leak required repeat surgery, while 2 patients required permanent CSF diversion for acquired hydrocephalus related to subarachnoid hemorrhage. Among the 72 patients who presented with visual impairment, 53 had improvement and 3 had visual worsening related to the surgery. 84% GTR.

Table 5: CSF Leak Closure Techniques

Author (Year)	Study Description	Classification Process / Evidence Class	Conclusions
Jho HD, Carrau RL (1997)[66]	Initial assessment of clinical outcomes following endoscopic endonasal transsphenoidal resection of 50 sellar lesions (19 NFPA)	Therapeutic / III	Early assessment of 50 patients who underwent endoscopic endonasal transsphenoidal surgery. Surgery for 19 NFPA cases were closed with autologous fat grafts for CSF leaks or large post-resection cavities. The fat grafts are supported with bone when possible or with absorbable buttress when bone could not be placed. With this technique, 1 postoperative CSF leak (5.3%) was reported in a recurrent pituitary adenoma with a large post-resection cavity. Bone could not be placed and the patient underwent re-operation, and the defect was repaired with a larger autologous fat graft. CSF diversion was not routinely used. For large sellar defects, and when intraoperative CSF leakage was encountered, a free abdominal fat graft was placed within the sellar cavity and anterior wall of the sella reconstructed with bone fragments. The lack of an appropriate control group renders this Class III evidence.

APPENDIX A

Search Strategies

Pubmed

1. (("Pituitary Neoplasms/surgery"[Majr] OR "Adenoma, Chromophobe/surgery"[Majr] OR "Sella Turcica/surgery"[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 ((transsphenoidal OR sublabial OR endoscopic OR endoscopy OR microscopic OR endonasal OR craniotomy OR stereotaxy OR neuronavigation OR "intraoperative MRI") AND surgery)
5. NOT Comment[pt] NOT Letter[pt]
6. Limit 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)