Congress of Neurological Surgeons

GUIDELINES

CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINES ON THE MANAGEMENT OF PATIENTS WITH NONFUNCTIONING PITUITARY ADENOMAS: INTRODUCTION AND METHODOLOGY

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)

Manish K. Aghi, MD, PhD[1], Mary E. Bodach, MLIS[2], Luis M. Tumialan MD[3], Nelson M. Oyesiku, MD, PhD[4], Chirag G. Patil, MD[5], Zachary Litvack MD[6], Gabriel Zada, MD[7]

[1.] Department of Neurosurgery, University of California, San Francisco; San Francisco, California, USA
[2.] Guidelines Department, Congress of Neurological Surgeons, Schaumburg, Illinois , USA
[3.] Barrow Neurological Institute, Phoenix, Arizona, USA
[4.] Department of Neurosurgery, Emory University, Atlanta, Georgia, USA
[5.] Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, USA
[6.] Department of Neurosurgery, George Washington University, Washington, DC, USA
[7.] Department of Neurological Surgery, University of Southern California, Los Angeles, California, USA

Correspondence:

Manish K. Aghi, MD, PhD
Department of Neurosurgery
University of California
San Francisco, CA, 94143-0112
Email: aghim@neurosurg.ucsf.edu

Keywords

Nonfunctioning pituitary adenoma, guidelines

Abbreviations

NFPA = nonfunctioning pituitary adenoma
CSF = cerebrospinal fluid
AANS = American Association of Neurological Surgeons
CNS = Congress of Neurological Surgeons

ABSTRACT

Background: Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors.

Objective: To create evidence-based guidelines for the initial management of NFPAs.

Methods: A multidisciplinary taskforce comprised of physician volunteers and evidence-based medicine trained methodologists conducted a systematic review of the literature relevant to the management of NFPAs. To ascertain the class of evidence for the post-treatment follow-ups, the task force used the Clinical Assessment evidence-based classification.

Results: Seven topics of importance were chosen for detailed evaluation. The topics addressed include preoperative evaluation, primary treatment, treatment options for residual tumors after surgery, and postoperative patient management. For preoperative patient evaluation, the guideline task force focused on preoperative imaging, preoperative laboratory evaluation, and preoperative ophthalmologic evaluation. For primary treatment, this guideline addresses surgical resection; medical therapy; radiation therapy; the natural history of untreated tumors; surgical methodologies, such as endoscopy, microscopy, or craniotomy; and intraoperative adjuncts like neuro-navigation, cerebrospinal (CSF) diversion, or intraoperative imaging. For residual tumor treatment, the guideline task force evaluated radiation versus observation. Additional topics addressed in this guideline regarding postoperative patient management include the frequency of postoperative imaging, postoperative endocrine evaluation, and postoperative ophthalmologic evaluation.

Conclusions: Although there is clearly a need for more randomized trials generating higher levels of evidence to help guide physicians managing NFPAs, the existing evidence provided valuable data upon which the guidelines described in the seven articles generated from this effort are based.

BACKGROUND

Patient Population

Patients with nonfunctioning pituitary adenomas (NFPAs) are evaluated in the chapters of this evidence-based clinical practice guideline.

Burden of Disease

No studies to date have investigated the disease burden or impact as measured by financial cost, symptomatic impact, or treatment morbidity of NFPAs expressed in quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) as measures to quantify the number of years lost due to disease.

Etiology

The molecular etiology and epidemiologic risk factors associated with NFPA development remain incompletely defined[1] and are not investigated in these articles.

Incidence and Prevalence

Estimates from cancer registries suggest that pituitary adenomas are uncommon (prevalence is 19 to 28 cases per 100,000 people), particularly compared to solid tumors like breast, lung, and colon cancer.[2] In contrast, a meta-analysis of autopsy data and radiologic studies performed in healthy volunteers indicates that pituitary adenomas are 700 times more common than registry data suggests and are found in 14% of autopsies and 23% of CT/MRI studies, giving a mean prevalence of 17%, or 1 in 6 people with pituitary tumors and 1 in 600 with macroadenomas.[3]

Risk Factors

The risk factors associated with NFPA development remain incompletely defined[1] and are not addressed in the chapters included in this guideline.

Topics Addressed

The topics addressed in this guideline include: preoperative evaluation, primary treatment, treatment options for residual tumors after surgery, and postoperative patient management. For preoperative patient evaluation, the Task Force focused on preoperative imaging, preoperative laboratory evaluation, and preoperative ophthalmologic evaluation. For primary treatment, this guideline addresses surgical resection; medical therapy; radiation therapy; the natural history of untreated tumors; surgical methodologies such as endoscopy, microscopy, or craniotomy; and intraoperative adjuncts like neuro-navigation, CSF diversion, or intraoperative imaging. For residual tumor treatment, the Task Force evaluated radiation versus observation. Additional topics addressed in this guideline regarding postoperative patient management include the

frequency of postoperative imaging, postoperative endocrine evaluation, and postoperative ophthalmologic evaluation.

PROCESS OVERVIEW

A multidisciplinary Task Force comprised of physician volunteers and evidence-based medicine trained methodologists conducted a systematic review of the literature relevant to the management of nonfunctioning pituitary adenomas (NFPAs). The physician volunteers represented neurosurgeons, neuro-ophthalmologists, neuroradiologists, and endocrinologists with expertise in pituitary adenomas. The evidence-based medicine trained methodologists had previous experience in guidelines production for the Joint Guidelines Committee (JGC) of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS). Additional details of the systematic review are provided below. During the development process, the task force participated in a series of conference calls and meetings. Multiple iterations of written review were conducted by the individuals of the panel and various CNS/AANS Committees prior to approval.

Guideline Task Force Panel Consensus and Guideline Approval Process

The guideline task force panel included context experts from multiple disciplines and various areas of therapy to address the topics addressed in this guideline. Sub-task force members were assigned to a specific chapter and were involved in the literature review, the creation and editing of the evidence tables, reviewing and voting of the final recommendations. The guideline draft was then circulated to the entire task force for final review and approval prior to submission for peer review by the JGC of the CNS and the AANS. Due to the reviewers' knowledge of evidence-based medicine and clinical practice guidelines methodology training, the JGC peer reviewers served as the journal's editorial reviewers. As a part of the JGC review process, the reviewers provided input on the content of the guideline and suggested revisions prior to approval and endorsement of the draft guideline by the CNS and AANS prior to publication. The development of this guideline was editorially independent from the funding agencies (CNS Executive Committee, and AANS/CNS Joint Tumor Section Executive Committee), the CNS and Joint Tumor Section.

METHODOLOGY

Literature Searches

The guideline task force collaborated with a medical librarian to search for articles published from January 1, 1966, to October 1, 2014. Searches were conducted in two electronic databases, PubMed and The Cochrane Central Register of Controlled Trials. Strategies for searching electronic databases were constructed by the guideline task force members and medical/research librarians using previously published search strategies to identify relevant studies. [4, 5, 6, 7, 8, 9, 10, 11] The root search strategies are provided in Appendix A and the chapter-specific search strategies are provided in the appendices of the individual chapters.

The searches of electronic databases were supplemented with manual screening of the bibliographies of all retrieved publications. The bibliographies of recent systematic reviews and other review articles for potentially relevant citations were also screened. All articles identified were subject to the study selection criteria listed below. As noted above, the guideline task force also examines lists of included and excluded studies for errors and omissions.

Article Inclusion Criteria

Articles were retrieved and included only if they met specific inclusion criteria. These criteria were also applied to articles provided by the evidence-based clinical practice guideline task force members who supplemented the electronic database searches with manual searches of the bibliographies. To reduce bias, these criteria were specified *a priori* before conducting the literature searches. For the purposes of this guideline, articles had to meet the following criteria to be included as evidence to support the recommendations presented in this guideline:

- Investigated patients suspected of having a pituitary mass
- Enrolled patients ≥18 years of age
- Either enrolled exclusively NFPA patients OR combined the results of patients with NFPAs and functioning pituitary adenomas and/or other pituitary masses with ≥ 90% of the patients having NFPAs
- Was a full article report of a clinical study
- If a prospective case series, reported baseline values
- Appeared in a peer-reviewed publication
- Enrolled ≥10 *NFPA* patients per arm per intervention (20 total) for each outcome
- Was of humans
- Was published in or after 1966
- Quantitatively presented results.

Article Exclusion Criteria

Articles of the following types were excluded as evidence to support the recommendations presented in this guideline:

- In vitro studies
- Studies performed on cadavers

- Studies not published in English
- Medical records reviews, meeting abstracts, historical articles, editorial, letters, or commentaries
- Systematic reviews, meta-analyses, or guidelines developed by others

Rating the Quality of the Evidence and Levels of Recommendations

The quality and classification of evidence (i.e., Class I, II, or III) was rated using an evidence hierarchy developed by the AANS/CNS Guidelines Committee for each of four different study types: therapeutic, prognostic, diagnostic, and economic or decision modeling. The methodology used to conduct quality evaluations of the evidence can be located by using the following link: https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology . The level/strength of recommendation (i.e., Level I, II, or III) was linked to the quality of the overall body of evidence included in the chapter and in support of a given recommendation. Please see Table 1 for the hierarchy classification of evidence on therapeutic effectiveness.

Strength of Recommendations Rating Scheme

Level I: High degree of clinical certainty (Class I evidence or overwhelming Class II evidence).

Level II: Clinical certainty (Class II evidence or a strong consensus of Class III evidence).

Level III: Clinical uncertainty (inconclusive or conflicting evidence or opinion).

Revision Plans

The guideline task force will monitor potentially relevant publications following the publication of this guideline and will revise the guideline and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations."[12] Also, in accordance with the Institute of Medicine's standards for developing trustworthy clinical practice guidelines, the task force will confirm within five years from the date of publication that the content included in the guideline is current clinical practice and the available technologies for the management of patients with nonfunctioning pituitary adenomas.

Statistical Methods

In Chapter 7, there was sufficient quality and quantity of literature to allow for a more detailed statistical analysis beyond the basic methods described above. Additional information regarding the type of analysis conducted and used to support the conclusions of this chapter are described in the methods sections of Chapter 7.

Voting on the Recommendations

The Task Force used a structured voting technique to finalize and approve the final recommendations, language, and strength of recommendations, presented in this review. The voting technique is referred to as the nominal group technique and described in an article by Murphy et al.[13] This technique includes up to three rounds of voting, using secret ballots to ensure Task Force members are blinded to the responses of other task force members. All the recommendations in this review were approved following the first round of voting and no further discussion was needed to finalize the recommendations described below. During the course of editing and finalization of the document, changes were made to allow recommendations to conform to the rules of evidence and language as described above. When this occurred, the changes were reviewed and approved by the group.

Disclosure of Funding

These evidence-based clinical practice guidelines were funded exclusively by the CNS and the Tumor Section of the CNS and the AANS, which received no funding from outside commercial sources to support the development of this document.

Acknowledgments

The authors acknowledge the CNS Guidelines Committee for their contributions throughout the development of the guideline, the AANS/CNS Joint Guidelines Committee for their review, comments, and suggestions throughout peer review, and Pamela Shaw, MSLIS, MS, for assistance with the literature searches. Also, the authors acknowledge the following individual peer reviewers for their contributions: Sepideh Amin-Hanjani, MD, Kathryn Holloway, MD, Odette Harris, MD, Brad Zacharia, MD, Daniel Hoh, MD, Isabelle Germano, MD, Martina Stippler, MD, Kimon Bekelis, MD, Christopher Winfree, MD, and William Mack, MD. Lastly, and most significantly, the authors would like to acknowledge Edward Laws, MD, for serving as an advisor on this nonfunctioning adenoma guidelines project and providing comprehensive critical appraisal.

Disclosure of 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. 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 authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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.

REFERENCES

1. Melmed S. Pathogenesis of pituitary tumors. *Nat. Rev. Endocrinol.* May 2011;7(5):257-266.

2. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T. Prevalence estimates for primary brain tumors in the united states by behavior and major histology groups. *Neuro Oncol.* Jul 2001;3(3):152-158.

3. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: A systematic review. *Cancer.* Aug 1 2004;101(3):613-619.

4. Kastner M, Wilczynski NL, Walker-Dilks C, McKibbon KA, Haynes B. Age-specific search strategies for medline. *J Med Internet Res.* 2006;8(4):e25.

5. Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR, Hedges T. Optimal search strategies for retrieving scientifically strong studies of treatment from medline: Analytical survey. *BMJ (Clinical research ed.).* May 21 2005;330(7501):1179.

6. Montori VM, Wilczynski NL, Morgan D, Haynes RB, Hedges T. Optimal search strategies for retrieving systematic reviews from medline: Analytical survey. *BMJ (Clinical research ed.).* Jan 8 2005;330(7482):68.

7. Wong SS, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in medline and embase. *J Med Libr Assoc.* Oct 2006;94(4):451-455.

8. Zhang L, Ajiferuke I, Sampson M. Optimizing search strategies to identify randomized controlled trials in medline. *BMC Med. Res. Methodol.* 2006;6:23.

9. Topfer LA, Parada A, Menon D, Noorani H, Perras C, Serra-Prat M. Comparison of literature searches on quality and costs for health technology assessment using the medline and embase databases. *Int. J. Technol. Assess. Health Care.* Spring 1999;15(2):297-303.

10. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in medline: An analytic survey. *BMC Med.* Jun 9 2004;2:23.

11. Wilczynski NL, Haynes RB, Hedges T. Embase search strategies achieved high sensitivity and specificity for retrieving methodologically sound systematic reviews. *Journal of clinical epidemiology.* Jan 2007;60(1):29-33.

12. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. *JAMA.* Jan 9 2013;309(2):139-140.

13. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health technology assessment (Winchester, England).* 1998;2(3):i-iv, 1-88.

TABLES

Table 1. Classification of Evidence

Evidence Classification for Therapeutic Studies	
Class I	Evidence provided by one or more well-designed randomized controlled clinical trials, including overview (meta-analyses) of such trials
Class II	Evidence provided by well-designed observational studies with concurrent controls (e.g. case control and cohort studies)
Class III	Evidence provided by expert opinion, case series, case reports and studies with historical controls
Evidence Classification for Diagnostic Studies	
Class I	Evidence provided by one or more well-designed clinical studies of a diverse population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and where applicable, likelihood ratios.
Class II	Evidence provided by one or more clinical studies of a restricted population using a "gold standard" reference test in a blinded evaluation of diagnostic accuracy and enabling assessment of sensitivity, specificity, positive and negative predictive values, and where applicable, likelihood ratios.
Class III	Evidence provided by expert opinion, studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and where applicable, likelihood ratios.
Evidence Classification for Clinical Assessment Studies	
Class I	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a **Kappa statistic ≥ 0.60. The Kappa statistic is defined as (po-pe)/(1-pe) where po is the relative observed agreement and pe is the hypothetical probability of chance agreement.**
Class II	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a **Kappa statistic ≥ 0.40.**
Class III	Evidence provided by one or more well-designed clinical studies in which interobserver and/or intraobserver reliability is represented by a **Kappa statistic < 0.40.**
Evidence Classification for Prognostic Studies	
In order to evaluate papers addressing prognosis, five technical criteria are applied: • Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease? • Was patient follow-up sufficiently long and complete? • Were objective outcome criteria applied in a "blinded" fashion?	

• If subgroups with different prognoses were identified, was there adjustment for important prognostic factors? • If specific prognostic factors were identified, was there validation in an independent “test set” group of patients? If all five of these criteria are satisfied, the evidence is classified as Class I. If four out of five are satisfied, the evidence is Class II, and if less than 4 are satisfied, it is Class III.	
Class I	All 5 technical criteria above are satisfied.
Class II	Four of five technical criteria are satisfied.
Class III	Everything else.

APPENDIX A

Search Strategies

PUBMED ROOT SEARCH

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)

Limit to English, Human studies, publication date 1/1/1966-10/1/2014

ALTERNATE PUBMED ROOT SEARCH FOR CHAPTERS 5–7

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

Limit to English, Human studies, publication date 1/1/1966-10/1/2014

COCHRANE LIBRARY SEARCH

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)